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 NEWS  4  MAY 10  CA/CAplus enhanced with 1900-1906 U.S. patent records
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 NEWS  6  MAY 19  Derwent World Patents Index to be reloaded and enhanced
 NEWS  7  MAY 30  IPC 8 Rolled-up Core codes added to CA/CAplus and
                  USPATFULL/USPAT2
 NEWS  8  MAY 30  The F-Term thesaurus is now available in CA/CAplus
 NEWS  9  JUN 02  The first reclassification of IPC codes now complete in
                  INPADOC
 NEWS 10  JUN 26  TULSA/TULSA2 reloaded and enhanced with new search and
                  and display fields
 NEWS 11  JUN 28  Price changes in full-text patent databases EPFULL and PCTFULL
 NEWS 12  JUl 11  CHEMSAFE reloaded and enhanced
 NEWS 13  JUl 14  FSTA enhanced with Japanese patents
 NEWS 14  JUl 19  Coverage of Research Disclosure reinstated in DWPI
 NEWS 15  AUG 09  INSPEC enhanced with 1898-1968 archive
 NEWS 16  AUG 28  ADISCTI Reloaded and Enhanced
 NEWS 17  AUG 30  CA(SM)/CAplus(SM) Austrian patent law changes
 NEWS 18  SEP 11  CA/CAplus enhanced with more pre-1907 records

 NEWS EXPRESS  JUNE 30 CURRENT WINDOWS VERSION IS V8.01b, CURRENT
               MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP),
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                                                      ENTRY    SESSION
FULL ESTIMATED COST                                    0.21       0.21
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=> L-685,458/cn
L1 0 L-685,458/CN

=> file caplus biosis medline embase

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	5.20	8.56

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=> L-685,458 or DAPT or DAPM or JLK-6 or OM99-2 or Z-VLL-CHO or GL189 or
"P10-P4'statV"

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L2          538 L-685,458 OR DAPT OR DAPM OR JLK-6 OR OM99-2 OR Z-VLL-CHO OR
                GL189 OR "P10-P4'STATV"

=> cancer or tumor or "solid tumor" or glioma or angiogenesis
L3      4389471 CANCER OR TUMOR OR "SOLID TUMOR" OR GLIOMA OR ANGIOGENESIS

=> l2 and l3
L4           41 L2 AND L3

=> dup rem l4
PROCESSING COMPLETED FOR L4
L5           29 DUP REM L4 (12 DUPLICATES REMOVED)

=> d ibib abs total

L5   ANSWER 1 OF 29     MEDLINE on STN
ACCESSION NUMBER:   2006100694     MEDLINE
DOCUMENT NUMBER:    PubMed ID: 16365048
TITLE:              Target selectivity of vertebrate notch proteins.
                    Collaboration between discrete domains and CSL-binding site
                    architecture determines activation probability.
AUTHOR:             Ong Chin-Tong; Cheng Hui-Teng; Chang Li-Wei; Ohtsuka
                    Toshiyuki; Kageyama Ryoichiro; Stormo Gary D; Kopan Raphael
CORPORATE SOURCE:   Department of Molecular Biology and Pharmacology, Division
                    of Dermatology, Washington University School of Medicine,
                    St. Louis, Missouri 63110, USA.
CONTRACT NUMBER:    GM55479-09 (NIGMS)
                    HD44056 (NICHD)
SOURCE:             The Journal of biological chemistry, (2006 Feb 24) Vol.
                    281, No. 8, pp. 5106-19.  Electronic Publication:
                    2005-12-19.
                    Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY:       United States
DOCUMENT TYPE:      Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:           English
FILE SEGMENT:       Priority Journals
ENTRY MONTH:        200605
ENTRY DATE:         Entered STN: 22 Feb 2006
                    Last Updated on STN: 5 May 2006
                    Entered Medline: 4 May 2006
AB   All four mammalian Notch proteins interact with a single DNA-binding
     protein (RBP-jkappa), yet they are not equivalent in activating target
     genes.  Parallel assays of three Notch-responsive promoters in several
     cell lines revealed that relative activation strength is dependent on
     protein module and promoter context more than the cellular context.  Each
     Notch protein reads binding site orientation and distribution on the
     promoter differently; Notch1 performs extremely well on paired sites, and
     Notch3 prefers single sites in conjunction with a proximal zinc finger
     transcription factor.  Although head-head sites can elicit a Notch
     response on their own, use of CBS (CSL binding site) in tail-tail
     orientation is context-dependent.  Bias for specific DNA elements is
     achieved by interplay between the N-terminal RAM (RBP-jkappa-associated
     molecule/ankyrin region), which interprets CBS proximity and orientation,
     and the C-terminal transactivation domain that interacts specifically with
     the transcription machinery or nearby factors.  To confirm the prediction
     that modular design underscores the evolution of functional divergence
     between Notch proteins, we generated a synthetic Notch protein (Notch1
     ankyrin with Notch3 transactivation domain) that displayed superior
     signaling strength on the hes5 promoter.  Consistent with the prediction
     that "preferred" targets (Hes1) should respond faster and at lower Notch
     concentration than other targets, we showed that Hes5-GFP was extinguished
     fast and recovered slowly, whereas Hes1-GFP was inhibited late and
     recovered quickly after a pulse of DAPT in metanephroi cultures.

L5   ANSWER 2 OF 29  CAPLUS  COPYRIGHT 2006 ACS on STN DUPLICATE 1
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ACCESSION NUMBER: 2006:503072 CAPLUS
TITLE: Collagen type I selectively activates ectodomain shedding of the discoidin domain receptor 1: involvement of Src tyrosine kinase
AUTHOR(S): Slack, Barbara E.; Siniaia, Marina S.; Blusztajn, Jan K.
CORPORATE SOURCE: Department of Pathology and Laboratory Medicine, Boston University School of Medicine, Boston, MA, 02118, USA
SOURCE: Journal of Cellular Biochemistry (2006), 98(3), 672-684
CODEN: JCEBD5; ISSN: 0730-2312
PUBLISHER: Wiley-Liss, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The discoidin domain receptor 1 (DDR1) is a receptor tyrosine kinase that is highly expressed in breast carcinoma cells. Upon binding to collagen, DDR1 undergoes autophosphorylation followed by limited proteolysis to generate a tyrosine phosphorylated C-terminal fragment (CTF). Although it was postulated that this fragment is formed as a result of shedding of the N-terminal ectodomain, collagen-dependent release of the DDR1 extracellular domain has not been demonstrated. We now report that, in conjunction with CTF formation, collagen type I stimulates concentration-dependent, saturable shedding of the DDR1 ectodomain from two carcinoma cell lines, and from transfected cells. In contrast, collagen did not promote cleavage of other transmembrane proteins including the amyloid precursor protein (APP), ErbB2, and E-cadherin. Collagen-dependent tyrosine phosphorylation and proteolysis of DDR1 in carcinoma cells were reduced by a pharmacol. Src inhibitor. Moreover, expression of a dominant neg. Src mutant protein in human embryonic kidney cells inhibited collagen-dependent phosphorylation and shedding of co-transfected DDR1. The hydroxamate-based metalloproteinase inhibitor TAPI-1 (tumor necrosis factor-α protease inhibitor-1), and tissue inhibitor of metalloproteinase (TIMP)-3, also blocked collagen-evoked DDR1 shedding, but did not reduce levels of the phosphorylated CTF. Neither shedding nor CTF formation were affected by the γ-secretase inhibitor, L-685,458. The results demonstrate that collagen-evoked ectodomain cleavage of DDR1 is mediated in part by Src-dependent activation or recruitment of a matrix- or disintegrin metalloproteinase, and that CTF formation can occur independently of ectodomain shedding. Delayed shedding of the DDR1 ectodomain may represent a mechanism that limits DDR1-dependent cell adhesion and migration on collagen matrixes.

REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 3 OF 29 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:76375 CAPLUS
DOCUMENT NUMBER: 142:148791
TITLE: Compounds and methods for promoting angiogenesis using a γ-secretase inhibitor or inhibiting the γ-secretase pathway
INVENTOR(S): Hellstrom, Mats; Karlsson, Linda; Wallgard, Elisabet
PATENT ASSIGNEE(S): Angiogenetics Sweden AB, Swed.
SOURCE: PCT Int. Appl., 29 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005008250	A1	20050127	WO 2004-SE1146	20040721
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH,				

CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
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EP 1671129 A1 20060621 EP 2004-749182 20040721
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, FI, RO, CY, TR, BG, CZ, EE, HU, PL, SK

PRIORITY APPLN. INFO.: SE 2003-2111 A 20030721
US 2003-488345P P 20030721
WO 2004-SE1146 W 20040721

AB Angiogenesis may be initiated or increased through the use of γ-secretase inhibitors. The γ-secretase inhibitor DAPT (N-[N-(3,5-Difluorophenacetyl-L-alanyl)]-S-phenylglycine t-Bu Ester) can initiate and increase angiogenesis. Methods for initiating and increasing angiogenesis are used for disease prevention and treatment as well as for generating research models.

REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 4 OF 29 MEDLINE on STN
ACCESSION NUMBER: 2005135165 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15766262
TITLE: Transition-state analogue gamma-secretase inhibitors stabilize a 900 kDa presenilin/nicastrin complex.
AUTHOR: Evin Genevieve; Canterford Louise D; Hoke David E; Sharples Robyn A; Culvenor Janetta G; Masters Colin L
CORPORATE SOURCE: Department of Pathology, The University of Melbourne, Parkville 3010, and The Mental Health Research Institute, Parkville 3052, Australia.. gmevin@unimelb.edu.au
CONTRACT NUMBER: AG05887 (NIA)
SOURCE: Biochemistry, (2005 Mar 22) Vol. 44, No. 11, pp. 4332-41. Journal code: 0370623. ISSN: 0006-2960.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200505
ENTRY DATE: Entered STN: 16 Mar 2005
Last Updated on STN: 26 May 2005
Entered Medline: 25 May 2005

AB Gamma-secretase mediates the final step, which generates Alzheimer's disease Abeta amyloid protein, by cleaving the transmembrane domain of the amyloid-beta protein precursor. Four gene products, presenilin, nicastrin, APH-1, and PEN-2, are required for gamma-secretase activity that is contained within a high molecular mass complex. To further characterize gamma-secretase, we probed membranes from human neuroblastoma SH-SY5Y cells with gamma-secretase inhibitor biotin derivatives of L-685,458, pepstatin A, and the difluoro alcohol 1-Bt. These inhibitor derivatives bound and precipitated PS1 fragments from membrane CHAPSO extracts. Analysis of PS1 complexes by blue native gel electrophoresis and western blotting indicated that the CHAPSO extracts contained complexes of approximately 900, 500, and 400 kDa. With this technique, derivatives of the three inhibitors were detected only in association with the 900 kDa species. Size-exclusion chromatography showed that 13% of PS1 immunoreactivity extracted with CHAPSO was comprised within a >or=900 kDa species with the remaining eluting in fractions of 669-250 kDa but that most enzymatic activity was associated with the 900 kDa fractions. After treatment with L-685,458 inhibitor, 49% PS1 immunoreactivity was eluted

in the 900 kDa fraction, supporting evidence that the inhibitor stabilized this complex. Subcellular fractionation of SH-SY5Y cells indicated that the 900 kDa complex was formed as PS1 and NCT matured through the secretory pathway and that enzymatic activity correlated with complex maturation. From these observations, we propose a model for the structure of active gamma-secretase that would consist of dimerization of 400-500 kDa subunits and be consistent with the apparent molecular mass of the complex.

L5 ANSWER 5 OF 29 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:524116 CAPLUS
DOCUMENT NUMBER: 143:419827
TITLE: Inducible nitric oxide synthase up-regulates Notch-1 in mouse cholangiocytes: implications for carcinogenesis
AUTHOR(S): Ishimura, Norihisa; Bronk, Steven F.; Gores, Gregory J.
CORPORATE SOURCE: Division of Gastroenterology and Hepatology, Mayo Clinic, College of Medicine, Rochester, MN, USA
SOURCE: Gastroenterology (2005), 128(5), 1354-1368
CODEN: GASTAB; ISSN: 0016-5085
PUBLISHER: Elsevier Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Inflammatory mediators and cell fate genes, such as the Notch gene family, both have been implicated in cancer biol. Because cholangiocarcinomas arise in a background of inflammation and express the inflammatory mediator inducible nitric oxide synthase (iNOS), we aimed to determine whether iNOS expression alters Notch expression and signaling. Notch receptor and ligand expression in human liver was evaluated by immunohistochem. The effect of iNOS and NO on Notch-1 expression was examined in cell lines. Notch-1, but not other Notch receptors, were up-regulated by cholangiocytes in primary sclerosing cholangitis and cholangiocarcinoma. The colocalization of Notch-1 and iNOS also was observed in large bile ducts from the hilar region of primary sclerosing cholangitis patients. Notch-1 expression in murine cholangiocytes was iNOS dependent. INOS expression also facilitated Notch signaling by inducing the nuclear translocation of its intracellular domain and the expression of a transcriptional target, hairy and enhancer of split (Hes)-1. The γ-secretase inhibitor N-[N-(3,5-Difluorophenacetyl-L-alanyl)-S-phenylglycine]t-Bu ester, which blocks Notch signaling, enhanced tumor necrosis factor-related apoptosis-inducing ligand-induced apoptosis in cholangiocarcinoma cells. These data implicate a direct link between the inflammatory mediator iNOS and Notch signaling, and have implications for the development and progression of cholangiocarcinoma.
REFERENCE COUNT: 52 THERE ARE 52 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 6 OF 29 CAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 2
ACCESSION NUMBER: 2005:1210892 CAPLUS
DOCUMENT NUMBER: 144:48725
TITLE: Blockade of γ-secretase activity within the hippocampus enhances long-term memory
AUTHOR(S): Dash, Pramod K.; Moore, Anthony N.; Orsi, Sara A.
CORPORATE SOURCE: The Vivian L. Smith Center for Neurologic Research and Department of Neurobiology and Anatomy, The University of Texas Medical School, Houston, TX, 77225, USA
SOURCE: Biochemical and Biophysical Research Communications (2005), 338(2), 777-782
CODEN: BBRCA9; ISSN: 0006-291X
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The γ-secretase complex, a membrane-bound aspartyl protease, hydrolyzes the transmembrane domains of several integral membrane proteins

including the key signaling mols. amyloid precursor protein (APP), Notch, deleted in colorectal cancer (DCC), and N- and E-cadherins. The proteolysis processing of these proteins is critical for generation of signaling mols. that may participate in neuronal communication and plasticity. Using a potent γ-secretase inhibitor, L-685,458, we examined if blockade of its activity in the hippocampus can influence contextual and spatial memory in rats. Surprisingly, we observed that post-training blockade of γ-secretase activity leads to enhanced long-term memory in two hippocampus-dependent tasks. This suggests that a signaling mol.(s) generated by γ-secretase activity may have a neg. influence on long-term memory formation.

REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 7 OF 29 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2005:151648 CAPLUS
DOCUMENT NUMBER: 142:456393
TITLE: Effects of the histone deacetylase inhibitor valproic acid on Notch signalling in human neuroblastoma cells
AUTHOR(S): Stockhausen, M-T.; Sjoelund, J.; Manetopoulos, C.; Axelson, H.
CORPORATE SOURCE: Department of Laboratory Medicine, Division of Molecular Medicine, Lund University, Malmoe, S-205 02, Swed.
SOURCE: British Journal of Cancer (2005), 92(4), 751-759
CODEN: BJCAAI; ISSN: 0007-0920
PUBLISHER: Nature Publishing Group
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Neuroblastoma (NB), a sympathetically derived childhood tumor, shows characteristics of neuronal precursor cells, suggesting a halted differentiation process. We have previously shown that the Notch signalling cascade, a key player during normal neurogenesis, also might be involved in NB differentiation. Valproic acid (VPA), a well-tolerated antiepileptic drug, has been shown to induce differentiation and cell death of NB cells, possibly associated with its recently described HDAC inhibiting activity. Stimulation of NB cells with VPA led to increased cell death and phenotypic changes associated with differentiation, i.e., neurite extension and upregulation of neuronal markers. VPA treatment also led to an activated Notch signalling cascade as shown by increased levels of intracellular Notch-1 and Hes-1, mimicking the initial phase of induced differentiation. These results reinforce that VPA potentially could be used in differentiation therapy of NB and that the effects in part could be a consequence of interference with the Notch signalling cascade.

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ACCESSION NUMBER: 2006:182870 BIOSIS
DOCUMENT NUMBER: PREV200600184982
TITLE: Identification of ID4 as a cooperating second hit for T cell lymphoma development in PU.1 URE Delta/Delta mice.
AUTHOR(S): Owens, Bronwyn M. [Reprint Author]; Yu, Li; Steidl, Ulrich; Kutok, Jeffrey L.; Clayton, Linda K.; Wagner, Katharina; Iwasaki, Hiromi; Liu, Chunhui; Hackanson, Bibrn; Akashi, Koichi; Plass, Christoph; Tenen, Daniel G.; Rosenbauer, Frank
CORPORATE SOURCE: Harvard Univ, Inst Med, Boston, MA 02115 USA
SOURCE: Blood, (NOV 16 2005) Vol. 106, No. 11, Part 1, pp. 734A-735A.
Meeting Info.: 47th Annual Meeting of the American-Society-of-Hematology. Atlanta, GA, USA. December 10 -13, 2005. Amer Soc Hematol.

CODEN: BLOOAW. ISSN: 0006-4971.
DOCUMENT TYPE: Conference; (Meeting)
Conference; (Meeting Poster)
LANGUAGE: English
ENTRY DATE: Entered STN: 15 Mar 2006
Last Updated on STN: 15 Mar 2006

AB NOTCH1 was discovered through its involvement in the t(7;9) chromosomal translocation found in less than 1% of T-ALLs. Recent studies have demonstrated a broader involvement of NOTCH1 in human T-ALL. The majority of T-ALL patients have activating mutations that disrupt either the heterodimerization domain or the PEST domain of NOTCH1. We sought to determine whether these mutations are also acquired in mouse models of T-ALL. We have sequenced the heterodimerization domain and PEST domain of notch1 in our mouse model of TAL1-induced leukemia and have found that 74% of the tumors harbor activating mutations in notch1. Cell lines derived from these tumors undergo G(0)/G(1) arrest and often apoptosis when treated with a gamma-secretase inhibitor (DAPT). In addition, we found activating notch1 mutations in 38% of thymic lymphomas that occur in mice deficient for various combinations of the H2AX, p53 and Rag2 genes. Thus, notch1 mutations are often acquired as a part of the molecular pathogenesis of T-ALL occurring in mice predisposed to develop the disease because they are transgenic for overexpression of the tall oncogene or because they have lost key tumor suppressor genes known to promote genomic instability.

L5 ANSWER 9 OF 29 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 2006:182866 BIOSIS
DOCUMENT NUMBER: PREV200600184978
TITLE: Activating Notch1 mutations in mouse models of T-ALL.
AUTHOR(S): O'Neil, Jennifer [Reprint Author]; Calvo, Jennifer; McKenna, Keith; Krishnamoorthy, Veena; Aster, Jon C.; Bassing, Craig H.; Alt, Frederick W.; Kelliher, Michelle; Look, A. Thomas
CORPORATE SOURCE: Dana Farber Canc Inst, Dept Pediat Oncol, Boston, MA 02115 USA
SOURCE: Blood, (NOV 16 2005) Vol. 106, No. 11, Part 1, pp. 734A. Meeting Info.: 47th Annual Meeting of the American-Society-of-Hematology. Atlanta, GA, USA. December 10 -13, 2005. Amer Soc Hematol.
CODEN: BLOOAW. ISSN: 0006-4971.
DOCUMENT TYPE: Conference; (Meeting)
Conference; (Meeting Poster)
LANGUAGE: English
ENTRY DATE: Entered STN: 15 Mar 2006
Last Updated on STN: 15 Mar 2006

AB NOTCH1 was discovered through its involvement in the t(7;9) chromosomal translocation found in less than 1% of T-ALLs. Recent studies have demonstrated a broader involvement of NOTCH1 in human T-ALL. The majority of T-ALL patients have activating mutations that disrupt either the heterodimerization domain or the PEST domain of NOTCH1. We sought to determine whether these mutations are also acquired in mouse models of TALL. We have sequenced the heterodimerization domain and PEST domain of notchI in our mouse model of TALI-induced leukemia and have found that 74% of the tumors harbor activating mutations in notch1. Cell lines derived from these tumors undergo G(0)/G(1), arrest and often apoptosis when treated with a gamma-secretase inhibitor (DAPT). In addition, we found activating notch1 mutations in 38% of thymic lymphomas that occur in mice deficient for various combinations of the H2AX, p53 and Rag2 genes. Thus, notch1 mutations are often acquired as a part of the molecular pathogenesis of T-ALL occurring in mice predisposed to develop the disease because they are transgenic for overexpression of the tall oncogene or because they have lost key tumor suppressor genes known to promote genomic instability.

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ACCESSION NUMBER: 2006:181221 BIOSIS
DOCUMENT NUMBER: PREV200600183333
TITLE: Quantitative proteomic studies of gamma-secretase inhibition in Hodgkin lymphoma cells reveal novel insights into notch signaling.
AUTHOR(S): Wallentine, Jeremy C. [Reprint Author]; Crockett, David K.; Elenitoba-Johnson, Kojo S. J.; Lim, Megan S.
CORPORATE SOURCE: Univ Utah, Dept Pathol, Sch Med, Salt Lake City, UT 84112 USA
SOURCE: Blood, (NOV 16 2005) Vol. 106, No. 11, Part 1, pp. 283A. Meeting Info.: 47th Annual Meeting of the American-Society-of-Hematology. Atlanta, GA, USA. December 10 -13, 2005. Amer Soc Hematol.
CODEN: BLOOAW. ISSN: 0006-4971.
DOCUMENT TYPE: Conference; (Meeting)
Conference; (Meeting Poster)
LANGUAGE: English
ENTRY DATE: Entered STN: 15 Mar 2006
Last Updated on STN: 15 Mar 2006

AB Notch signaling has been implicated in the regulation of Hodgkin lymphoma (HL) survival via NF-kappaB. Notch signaling is dependent on the interaction of ligands with the transmembrane notch receptor. Ligand binding triggers proteolytic cleavage of the intracellular notch domain with subsequent translocation to the nucleus and activation of transcription factors. Gamma-secretase which catalyzes the protenlytic cleavage and release of the notch intracellular domain is critical in the mediation of notch signaling. Inhibition of gamma-secretase using 7 (N-[N-(3,5-difluorophenyl)-L-alanyl]-s-phenyl-glycine t-butyl ester) (DAFT) in rat fetal thymocytes significantly reduces the expression of notch target genes. We identified proteins released by HL-derived cells into conditioned media including multiple upstream and downstream components of the notch signaling cascade, specifically: notch 1, notch2, jagged1, jagged2, HES2, Hes4, GATA2 and GATA5. A proteomic analysis of the differentially expressed proteins among DAFT treated and untreated cells will reveal potential novel downstream mediators of notch signaling, increasing our understanding of HL pathogenesis. We sought to identify the proteomic consequences of notch signaling inhibition in L428 HL cells using a mass spectrometry-based proteomic approach. Treatment of L428 HL cells with DART (50 mu M) resulted in decreased cell proliferation as measured by the MTT assay which was associated with induction of p27Kip1. We utilized an endoproteinase catalyzed O16/O18 differential isotopic strategy to quantitatively determine the global proteomic changes following inhibition of the notch signaling pathway using DAFT. Proteins were collected from the cell lysate of treated and non-treated L428 cells, subjected to O16/O18 labeling and then analyzed by reverse-phase liquid chromatography coupled with electrospray ionization tandem mass spectrometry. A total of 156 proteins with 2 or more unique peptides were identified as being differentially expressed between treated and non-treated L428 cells. Proteins of diverse location and function were identified. Importantly a large number of proteins involved in transcription (12%; RelB, TRRAP, RB-associated protein, NCOR1), and located in the nucleus (27%; H2AO, FUSE binding protein 1, ANC5, SMYD1) were identified. Other important functional categories of the identified proteins included signaling activity (28%), and catalytic activity (41%). Several known proteins regulated by notch and involved with the regulation of notch activity such as (Histone acetyltransferase PCAF, RelB. N-COR1) were identified and found to be under expressed in treated cells. In addition, novel proteins with transcriptional and cell signaling activities have been identified, representing unique pathways that may be directly or indirectly affected by notch signaling. Our study represents the first comprehensive analysis of differentially expressed proteins following the inhibition of notch signaling. These results provide novel insights into our understanding of the pathogenesis and the role of notch signaling in HL.

L5 ANSWER 11 OF 29 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:387245 CAPLUS
DOCUMENT NUMBER: 143:625
TITLE: Inhibition of angiogenesis and tumor growth by β and γ-secretase inhibitors
AUTHOR(S): Paris, Daniel; Quadros, Amita; Patel, Nikunj; DelleDonne, Anthony; Humphrey, James; Mullan, Michael
CORPORATE SOURCE: Roskamp Institute, Sarasota, FL, 34243, USA
SOURCE: European Journal of Pharmacology (2005), 514(1), 1-15
CODEN: EJPHAZ; ISSN: 0014-2999
PUBLISHER: Elsevier B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The involvement of β-secretase and γ-secretase in producing the β-amyloid component of senile plaques found in the brain of Alzheimer's patients has fueled a major research effort to design selective inhibitors of these proteases. Interestingly, γ-secretase cleaves several proteins including Notch, E-cadherin, CD44 and ErbB-4 (erythroblastic leukemia viral oncogene homolog 4), which are important modulators of angiogenesis. The β-amyloid precursor protein, which is cleaved by β-secretase and γ-secretase to produce β-amyloid, is highly expressed in the endothelium of neoforming vessels suggesting that it might play a role during angiogenesis. These data prompted us to explore the effects of β and γ-secretase inhibitors of different structures on angiogenesis and tumor growth. Both the γ and β-secretase inhibitors tested reduce endothelial cell proliferation without inducing cellular toxicity, suppress the formation of capillary structures in vitro and oppose the sprouting of microvessel outgrowths in the rat aortic ring model of angiogenesis. Moreover, they potently inhibit the growth and vascularization of human glioblastoma and human lung adenocarcinoma tumors xenotransplanted into nude mice. Altogether these data suggest that the γ and β-secretases play an essential role during angiogenesis and that inhibitors of the β and γ-secretases may constitute new classes of anti-angiogenic and anti-tumoral compds.
REFERENCE COUNT: 51 THERE ARE 51 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 12 OF 29 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:718305 CAPLUS
DOCUMENT NUMBER: 141:236630
TITLE: Anti-angiogenic and anti-tumoral properties of beta and gamma secretase inhibitors
INVENTOR(S): Paris, Daniel; Mullan, Michael J.
PATENT ASSIGNEE(S): Roskamp Research LLC, USA
SOURCE: PCT Int. Appl., 44 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004073630	A2	20040902	WO 2004-US4494	20040218
WO 2004073630	A3	20050428		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN,

GQ, GW, ML, MR, NE, SN, TD, TG

AU 2004212965	A1	20040902	AU 2004-212965		20040218
CA 2516259	AA	20040902	CA 2004-2516259		20040218
US 2004229816	A1	20041118	US 2004-780905		20040218
EP 1596878	A2	20051123	EP 2004-712274		20040218
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK					
BR 2004007597	A	20060221	BR 2004-7597		20040218
CN 1777436	A	20060524	CN 2004-80010480		20040218
JP 2006517979	T2	20060803	JP 2006-503611		20040218
NO 2005004221	A	20051111	NO 2005-4221		20050912
PRIORITY APPLN. INFO.:			US 2003-319954P	P	20030218
			WO 2004-US4494	A	20040218

AB The present invention relates to methods of treating tumors or proliferative disorders that are associated with angiogenesis by administering g-secretase and b-secretase inhibitors that inhibit secretases involved in amyloid precursor protein processing. In particular, methods are provided to treat tumors or proliferative disorders, or to inhibit angiogenesis associated with tumors, proliferative or inflammatory disorders, in animals or humans in need of such treatment or angiogenic inhibition, by administering to the animal or human therapeutically effective amts. in unit dosage form of a composition containing a carrier and at least one g-secretase or b-secretase inhibitor that inhibits secretase APP processing.

L5 ANSWER 13 OF 29 CAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 3

ACCESSION NUMBER:	2004:63475 CAPLUS
DOCUMENT NUMBER:	140:161504
TITLE:	Notch Signaling and ERK activation are important for the osteomimetic properties of prostate cancer bone metastatic cell lines
AUTHOR(S):	Zayzafoon, Majd; Abdulkadir, Sarki A.; McDonald, Jay M.
CORPORATE SOURCE:	Department of Pathology, University of Alabama at Birmingham, Birmingham, AL, 35233, USA
SOURCE:	Journal of Biological Chemistry (2004), 279(5), 3662-3670 CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER:	American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE:	Journal
LANGUAGE:	English

AB Prostate cancer bone metastases are characterized by their ability to induce osteoblastic lesions and local bone formation. It has been suggested that bone metastatic prostate cancer cells are osteomimetic and capable of expressing genes and proteins typically expressed by osteoblasts. The ability of preosteoblasts to differentiate and express osteoblastic genes depends on several pathways, including Notch and MAPK. Here we show that notch1 expression is increased 4-5 times in C4-2B and MDA PCa 2b cells (osteoblastic skeletal prostate metastatic cancer cell lines) when compared with nonskeletal metastatic cell lines (LNCaP and DU145). Notch1 ligand, dll1, is expressed only in C4-2B cells. Immunohistochem. studies demonstrate that Notch1 is present in both human clin. samples from prostate cancer bone metastases and the C4-2B cell line. To determine whether prostate cancer bone metastases respond to osteogenic induction similar to osteoblasts, C4-2B cells were cultured in osteogenic medium that promotes mineralization. C4-2B cells mineralize and express HES-1 (a downstream target of Notch), an effect that is completely inhibited by L-685,458, a Notch activity inhibitor. Furthermore, osteogenic induction increases ERK activation, runx2 expression, and nuclear localization, independent of Notch signaling. Finally, we show that Notch and ERK activation are essential for Runx2 DNA binding activity and osteocalcin gene expression in C4-2B cells in response to osteogenic

induction. These studies demonstrate that prostate cancer bone metastatic cell lines acquire osteoblastic properties through independent activation of ERK and Notch signaling; presumably, both pathways are activated in the bone microenvironment.

REFERENCE COUNT: 49 THERE ARE 49 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 14 OF 29 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN

ACCESSION NUMBER: 2005:477542 BIOSIS
DOCUMENT NUMBER: PREV200510269446
TITLE: Notch signaling-dependant expulsion of parasites through mast cell-mediated immunity.
AUTHOR(S): Sakata-Yanagimoto, Mamiko [Reprint Author]; Yamaguchi-Nakagami, Etsuko; Sakai, Toru; Kumano, Keiki; Kunisato, Atsushi; Crcareva, Aleksandra; Kurokawa, Mineo; Ogawa, Seishi; Yasutomo, Koji; Hirai, Hisamaru; Chiba, Shigeru
CORPORATE SOURCE: Tokyo Univ Hosp, Dept Cell Therapy Transplantat Med, Tokyo 113, Japan
SOURCE: Blood, (NOV 16 2004) Vol. 104, No. 11, Part 1, pp. 412A. Meeting Info.: 46th Annual Meeting of the American-Society-of-Hematology. San Diego, CA, USA. December 04 -07, 2004. Amer Soc Hematol. CODEN: BLOOAW. ISSN: 0006-4971.
DOCUMENT TYPE: Conference; (Meeting)
Conference; (Meeting Poster)
LANGUAGE: English
ENTRY DATE: Entered STN: 16 Nov 2005
Last Updated on STN: 16 Nov 2005

AB [Background] Notch signaling is known to be important in hematopoiesis, but very little information is available about its significance in mast cells. Here we provide direct evidence that notch signaling is critical for both development and function of mast cells in vitro and in vivo. [Methods] A Lin(-) fraction of mouse bone marrow cells was cultured on immobilized Delta1 in the presence of SCF and IL-3, and emerging Lin(-)Fc epsilon RI(+)c-Kit(+) mast cells were characterized. Next, production of mouse mast cell protease-1 (mMCP-1), which is specific for nematode infection through locally expressed TGF-beta 1 in vivo, by bone marrow-derived mast cells (BMMC) was analyzed after the stimulation with Delta1 in the presence of TGF-beta 1. Finally, mice were infected with Strongyloides venezuelensis after pre-treatment with Delta1, and expulsion of the worms was examined. [Results] Lin(-)Fc epsilon RI(+)c-Kit(+) mast cells developed remarkably earlier if stimulated with Delta1 (at one week, 15% vs. 3%). DAPT, a gamma-secretase inhibitor, blocked the Delta1 effect, while it did not affect the regular time-course mast cell generation by SCF and IL-3. SB431542, a selectiveinhibitor of TGF-1 signaling, also blocked early mast cell generation by Delta1. Delta1 augmented mMCP-1 expression and secretion from BMMC by 50 fold. Both DAPT and SB431542 showed a dose-dependent inhibition of Delta1 effect on mMCP-1 expression and secretion. Pretreatment of the hosts with Delta1 promoted the expulsion of S. venezuelensis, (left/inoculated ratios of worms, 3% vs. 40%) while Delta1 had no effect in the mast cell-deficient W/Wv mice. [Discussion] Our observations reveal that notch signaling regulates both development and function of mast cells in vitro in conjunction with TGF-beta 1 signaling. In vivo, it is also likely that Delta1 facilitates the functional maturation of intestinal mast cells to eradicate parasites. More precise mechanism of Delta1 action on mast cells in vivo is under a study.[GRAPHICS]These purified monocytes also showed transdifferentiation into endothelial cells in the presence of PTN with m-CSF unlike cells treated with m-CSF-alone orcells without these factors present. We determined whether PTN could also stimulate differentiation of bone marrow stem cells into endothelial cells. The stem cells were derived from bone marrow selected for CD34 using magnetic bead selection, and were stimulated with either m-CSF or PTN alone or a

combinationof m-CSF and PTN or no treatment for 7 days. Real time PCR analysis showed that the m-CSF and PTN combination markedly increased endothelial cell marker expression and decreased monocyte marker (CD68 and c-fms) expression in this stem cell population. When induced with PTN alone, the stem cells exhibited slightly increasing expression of endothelial markers with no change in monocyte marker expression whereas m-CSF alone and no treatment had no effect on either endothelial or monocyte marker expression. These experiments define a previously unrecognized novel mechanism leading to angiogenesis in cancer patients- thetransdifferentiation of monocytes into endothelial cells by a factor highly produced by tumor cells. They also suggest a potential new specific target to inhibit angiogenesis-pleitrophin which may have profound clinical implications.

L5 ANSWER 15 OF 29 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 2004326678 EMBASE
TITLE: Notch signaling in neuroblastoma.
AUTHOR: Pahlman S.; Stockhausen M.-T.; Fredlund E.; Axelson H.
CORPORATE SOURCE: H. Axelson, Department of Laboratory Medicine, Division of Molecular Medicine, Lund Univ., Univ. Hosp. MAS, E., Malmo, Sweden. hakan.axelson@molmed.mas.lu.se
SOURCE: Seminars in Cancer Biology, (2004) Vol. 14, No. 5, pp. 365-373. .
Refs: 60
ISSN: 1044-579X CODEN: SECBE7
PUBLISHER IDENT.: S 1044-579X(04)00033-1
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 008 Neurology and Neurosurgery
021 Developmental Biology and Teratology
022 Human Genetics
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 2 Sep 2004
Last Updated on STN: 2 Sep 2004

AB Neuroblastoma is a pediatric tumor that originates from precursor cells of the sympathetic nervous system that have discontinued their normal differentiation program. This review is focused on involvement of the Notch signaling cascade in the process of differentiation in neuroblastoma cells and normal cells of the sympathetic nervous system. Hypoxia induces dedifferentiation of neuroblastoma cells in vivo and in vitro, and under oxygen-compromised conditions the Notch cascade is activated. This activation might promote development of the dedifferentiated phenotype. The implications of these observations for tumor biology are also discussed. .COPYRGT. 2004 Elsevier Ltd. All rights reserved.

L5 ANSWER 16 OF 29 MEDLINE on STN

ACCESSION NUMBER: 2004079750 MEDLINE
DOCUMENT NUMBER: PubMed ID: 14969346
TITLE: Effects of dopaminergic drugs on the mast cell degranulation and nitric oxide generation in RAW 264.7 cells.
AUTHOR: Seol Il-Woong; Kuo Na Youn; Kim Kyeong Man
CORPORATE SOURCE: Pharmacology Laboratory, College of Pharmacy, Drug Development Research Center, Chonnam National University, Kwang-Ju, Korea.
SOURCE: Archives of pharmacal research, (2004 Jan) Vol. 27, No. 1, pp. 94-8.
Journal code: 8000036. ISSN: 0253-6269.
PUB. COUNTRY: Korea (South)

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200411
ENTRY DATE: Entered STN: 19 Feb 2004
Last Updated on STN: 3 Nov 2004
Entered Medline: 2 Nov 2004

AB Effects of dopaminergic drugs on the degranulation of mast cells (RBL-2H3 cells) and the nitric oxide production from macrophage cells (RAW 264.7) were studied. Among the dopaminergic agonists and antagonists tested, bromocriptine, 7-OH-DPAT, haloperidol, and clozapine showed potent inhibitions of mast cell degranualtion (IC50 value, 5 microM). However, these dopaminergic agents did not affect the tyrosine phosphorylations of the signaling components of the high affinity IgE receptor (FcepsilonRI), such as Syk, PLCgamma1, and PLCgamma2.; This suggested that these signaling components were not involved in the inhibition of the mast cell degranulation by these compounds. On the other hand, dopamine, bromocriptine, 7-OH-DAPT, and haloperidol markedly inhibited the nitric oxide production from RAW 264.7 cells (IC50 values, 10-20 microM). Bromocriptine, a dopamine agonist that is routinely used for the treatment of Parkinsons disease, inhibited the expression of the inducible nitric oxide synthase at an early stage of the LPS-induced protein expression in a dose-dependent manner. The results suggested that these dopaminergic agents, when used for the treatment of dopamine receptors-related diseases, such as Schizophrenia or Parkinsons disease, might have additional beneficial effects.

L5 ANSWER 17 OF 29 MEDLINE on STN
ACCESSION NUMBER: 2003100609 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12493731
TITLE: Familial Alzheimer disease-linked presenilin 1 variants enhance production of both Abeta 1-40 and Abeta 1-42 peptides that are only partially sensitive to a potent aspartyl protease transition state inhibitor of "gamma-secretase".
AUTHOR: Ikeuchi Takeshi; Dolios Georgia; Kim Seong-Hun; Wang Rong; Sisodia Sangram S
CORPORATE SOURCE: Department of Neurobiology, Pharmacology and Physiology, The University of Chicago, Chicago, Illinois 60637, USA.
CONTRACT NUMBER: AG021494 (NIA)
AG10491 (NIA)
SOURCE: The Journal of biological chemistry, (2003 Feb 28) Vol. 278, No. 9, pp. 7010-8. Electronic Publication: 2002-12-19.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200304
ENTRY DATE: Entered STN: 5 Mar 2003
Last Updated on STN: 9 Apr 2003
Entered Medline: 8 Apr 2003

AB Presenilin 1 (PS1) plays an essential role in intramembranous "gamma-secretase" processing of several type I membrane proteins, including the beta-amyloid precursor proteins (APP) and Notch1. In this report, we examine the activity of two familial Alzheimer's disease-linked PS1 variants on the production of secreted Abeta peptides and the effects of L-685,458, a potent gamma-secretase inhibitor, on inhibition of Abeta peptides from cells expressing these PS1 variants. We now report that PS1 variants enhance the production and secretion of both Abeta1-42 and Abeta1-40 peptides. More surprisingly, whereas the IC(50) for inhibition of Abeta1-40 peptide production from cells expressing wild-type PS1 is approximately 1.5 microm, cells expressing the PS1deltaE9 mutant PS1 exhibit an IC(50) of approximately 4

microm. Immunoprecipitation and matrix-assisted laser desorption/ionization time-of-flight mass spectrometry reveal that the levels of Abeta1-43 peptides are elevated in medium of PS1deltaE9 cells treated with higher concentrations of inhibitor. The differential effects of wild-type and mutant PS1 on gamma-secretase production of Abeta peptides and the disparity in sensitivity of these peptides to a potent gamma-secretase suggest that PS may be necessary, but not sufficient, to catalyze hydrolysis at the scissile bonds that generate the termini of Abeta1-40 and Abeta1-42 peptides.

L5 ANSWER 18 OF 29 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN

ACCESSION NUMBER: 2004:235139 BIOSIS
DOCUMENT NUMBER: PREV200400234592
TITLE: Semicontinuous stationary suspension cultivation of human continuous cell lines maintained before in monolayer.
AUTHOR(S): Benjumovich, M. [Reprint Author]
CORPORATE SOURCE: Moscow State Medico-Stomatological University Hospital, Moscow, Russia
SOURCE: International Journal of Artificial Organs, (September 2003) Vol. 26, No. 9, pp. 817. print.
Meeting Info.: 1st World Congress on Regenerative Medicine. Leipzig, Germany. October 22-24, 2003.
CODEN: IJAODS. ISSN: 0391-3988.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 28 Apr 2004
Last Updated on STN: 28 Apr 2004

L5 ANSWER 19 OF 29 CAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 4

ACCESSION NUMBER: 2003:436167 CAPLUS
DOCUMENT NUMBER: 139:357709
TITLE: Aspartic peptidase inhibitors: Implications in drug development
AUTHOR(S): Dash, Chandravanu; Kulkarni, Aarohi; Dunn, Ben; Rao, Mala
CORPORATE SOURCE: Division of Biochemical Sciences, National Chemical Laboratory, Pune, 411008, India
SOURCE: Critical Reviews in Biochemistry and Molecular Biology (2003), 38(2), 89-119
CODEN: CRBBEJ; ISSN: 1040-9238
PUBLISHER: CRC Press LLC
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. The last decade has witnessed an effervescence of research interest in the development of potent inhibitors of various aspartic peptidases. As an enzyme family, aspartic peptidases are relatively a small group that has received enormous interest because of their significant roles in human diseases like involvement of renin in hypertension, cathepsin D in metastasis of breast cancer, β-Secretase in Alzheimer's Disease, plasmepsins in malaria, HIV-1 peptidase in acquired immune deficiency syndrome, and secreted aspartic peptidases in candidal infections. There have been developments on clin. active inhibitors of HIV-1 peptidase, which have been licensed for the treatment of AIDS. The inhibitors of plasmepsins and renin are considered a viable therapeutic strategy for the treatment of malaria and hypertension. Relatively few inhibitors of cathepsin D have been reported, partly because of its uncertain role as a viable target for therapeutic intervention. The β-secretase inhibitors OM99-2 and OM003 were designed based on the substrate specificity information. The present article is a comprehensive state-of-the-art review describing the aspartic peptidase inhibitors illustrating the recent developments in the area. In addition, the homologies between the reported inhibitor sequences have been analyzed. The understanding of the

structure-function relationships of aspartic peptidases and inhibitors will have a direct impact on the design of new inhibitor drugs.
REFERENCE COUNT: 179 THERE ARE 179 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 20 OF 29 MEDLINE on STN
ACCESSION NUMBER: 2003211080 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12732196
TITLE: Contribution of presenilin/gamma-secretase to calsenilin-mediated apoptosis.
AUTHOR: Jo Dong-Gyu; Chang Jae-Woong; Hong Hyun-Seok; Mook-Jung Inhee; Jung Yong-Keun
CORPORATE SOURCE: Department of Life Science, Kwangju Institute of Science and Technology, Kwangju 500-712, Republic of Korea.
SOURCE: Biochemical and biophysical research communications, (2003 May 23) Vol. 305, No. 1, pp. 62-6.
Journal code: 0372516. ISSN: 0006-291X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200306
ENTRY DATE: Entered STN: 7 May 2003
Last Updated on STN: 19 Jun 2003
Entered Medline: 18 Jun 2003
AB Mutant presenilins cause early-onset of familial Alzheimer's disease and render cells vulnerable to apoptosis. Calsenilin/DREAM/KChIP3 is a multifunctional calcium-binding protein that interacts with presenilin and mediates calcium-mediated apoptosis. In the present study, we report that the calsenilin-mediated apoptosis is regulated by presenilin. The expression of calsenilin was highly up-regulated in neuronal cells undergoing Abeta42-triggered cell death. The incidence of calsenilin-mediated apoptosis was diminished in presenilin-1(-/-) mouse embryonic fibroblast cells or neuronal cells stably expressing a loss-of-function presenilin-1 mutant. On the contrary, an array of familial Alzheimer's disease-associated presenilin mutants (gain-of-function) increased calsenilin-induced cell death. Moreover, gamma-secretase inhibitors, including compound E and DAPT, decreased the calsenilin-induced cell death. These results suggest that the pro-apoptotic activity of calsenilin coordinates with presenilin/gamma-secretase activity to play a crucial role in the neuronal death of Alzheimer's disease.

L5 ANSWER 21 OF 29 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 2002:336050 BIOSIS
DOCUMENT NUMBER: PREV200200336050
TITLE: Amyloid-lowering isocoumarins are not direct inhibitors of gamma-secretase.
AUTHOR(S): Esler, William P. [Reprint author]; Das, Chittaranjan [Reprint author]; Campbell, William A. [Reprint author]; Kimberly, W. Taylor [Reprint author]; Kornilova, Anna Y. [Reprint author]; Diehl, Thekla S. [Reprint author]; Ye, Wenjuan [Reprint author]; Ostaszewski, Beth L. [Reprint author]; Xia, Weiming [Reprint author]; Selkoe, Dennis J. [Reprint author]; Wolfe, Michael S. [Reprint author]
CORPORATE SOURCE: Center for Neurologic Diseases, Brigham and Women's Hospital and Harvard Medical School, 77 Avenue Louis Pasteur, Boston, MA, 02115, USA
mwolfe@rics.bwh.harvard.edu
SOURCE: Nature Cell Biology, (May, 2002) Vol. 4, No. 5, pp. E110-E111. print.
ISSN: 1465-7392.
DOCUMENT TYPE: Letter

LANGUAGE: English
ENTRY DATE: Entered STN: 12 Jun 2002
Last Updated on STN: 12 Jun 2002

L5 ANSWER 22 OF 29 MEDLINE on STN
ACCESSION NUMBER: 2002136366 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11851430
TITLE: A novel epsilon-cleavage within the transmembrane domain of the Alzheimer amyloid precursor protein demonstrates homology with Notch processing.
AUTHOR: Weidemann Andreas; Eggert Simone; Reinhard Friedrich B M; Vogel Markus; Paliga Krzysztof; Baier Gottfried; Masters Colin L; Beyreuther Konrad; Evin Genevieve
CORPORATE SOURCE: Zentrum fur Molekulare Biologie Heidelberg, INF 282, 69120 Heidelberg, Germany.
SOURCE: Biochemistry, (2002 Feb 26) Vol. 41, No. 8, pp. 2825-35. Journal code: 0370623. ISSN: 0006-2960.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200203
ENTRY DATE: Entered STN: 2 Mar 2002
Last Updated on STN: 3 Apr 2002
Entered Medline: 28 Mar 2002
AB Proteolytic processing of the transmembrane domain of the amyloid precursor protein (APP) is a key component of Alzheimer's disease pathogenesis. Using C-terminally tagged APP derivatives, we have identified by amino-terminal sequencing a novel cleavage site of APP, at Leu-49, distal to the gamma-secretase site. This was termed -cleavage. Brefeldin A treatment and pulse-chase experiments indicate that this cleavage occurs late in the secretory pathway. The level of -cleavage is decreased by expression of presenilin-1 mutants known to impair Abeta formation, and it is sensitive to the gamma-secretase inhibitors MDL28170 and L-685,458. Remarkably, it shares similarities with site 3 cleavage of Notch-1: membrane topology, cleavage before a valine, dependence on presenilins, and inhibition profile.

L5 ANSWER 23 OF 29 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 2003:356701 BIOSIS
DOCUMENT NUMBER: PREV200300356701
TITLE: Novel gamma-Secretase Inhibitor DAPT Blocks Activated Notch Signaling and Controls Tumor Cell Growth in Hodgkin and Anaplastic Large Cell Lymphoma.
AUTHOR(S): Jundt, Franziska [Reprint Author]; Arnold, Wolfgang [Reprint Author]; Mathas, Stephan [Reprint Author]; Wolfe, Michael [Reprint Author]; Forster, Reinhold [Reprint Author]; Dorken, Bernd [Reprint Author]
CORPORATE SOURCE: Universitatsklinikum Charite, Campus Virchow-Klinikum, Humboldt University of Berlin, Germany
SOURCE: Blood, (November 16 2002) Vol. 100, No. 11, pp. Abstract No. 594. print.
Meeting Info.: 44th Annual Meeting of the American Society of Hematology. Philadelphia, PA, USA. December 06-10, 2002. American Society of Hematology.
CODEN: BLOOAW. ISSN: 0006-4971.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
Conference; (Meeting Poster)
LANGUAGE: English
ENTRY DATE: Entered STN: 6 Aug 2003
Last Updated on STN: 6 Aug 2003
AB Notch receptors are key regulators of hematopoietic differentiation and development. Notch activation either induces stem cell renewal or

differentiation towards lymphoid lineages. Moreover, activation induces lymphoid precursors to become T cells rather than B cells. Truncated Notch alleles have further been implicated in the development of aggressive human T-cell leukemia. We recently showed, that Notch receptors are highly overexpressed in primary tumor cells of Hodgkin (25/25 cases) and anaplastic large cell (12/12 cases) lymphoma (Blood 2002; 99:3398-3403). In addition, we demonstrated a novel mechanism for the oncogenic capacity of Notch by showing that activation of Notch signaling by its ligand Jagged1, that was expressed in primary tumor cells as well as in neighboring cells in vivo (immunohistology, in situ hybridisation), resulted in dramatic increases in proliferation and apoptosis resistance of tumor cells of Hodgkin and anaplastic large cell lymphoma. Already highly proliferating tumor cells could exponentially increase their proliferation rates up to 2- or even 3-fold in 20h after Notch activation. Therefore, our data provided evidence, that activation of Notch signaling is essential for the growth and survival of the tumor cells in vitro and that inhibition of Notch signaling in vivo might be a novel therapeutic approach in Hodgkin and anaplastic large cell lymphoma. In this study, we established a xenotransplant model in SCID mice, where we injected the Hodgkin cell line KM-H2 subcutaneously. KM-H2 cells were not tumorigenic in SCID mice within three months (0/8 mice). However, activation of Notch signaling by irradiated Jagged1-expressing cells dramatically increased tumor cell growth of KM-H2 cells (8/11 mice). These data indicate that activated Notch signaling essentially contributes to Hodgkin lymphomagenesis in vivo. Furthermore, we used the functional gamma-secretase inhibitor DAPT to block activated Notch signaling in tumor cells of Hodgkin and anaplastic large cell lymphoma. gamma-secretase catalyzes the release of the intracellular domain of Notch that then translocates to the nucleus to activate expression of downstream genes. Inhibition of gamma-secretase activity is currently investigated as a therapeutic strategy in Alzheimer's disease, because gamma-secretase similarly cleaves amyloid precursor proteins to release Abeta peptides, accumulation of which is causally related to Alzheimer's disease. DAPT was already shown to potently reduce beta-amyloid levels in brain in mouse models of Alzheimer's disease. We tested DAPT activity in proliferation assays in which tumor cells of Hodgkin (L1236, HD-LM2) and anaplastic large cell lymphoma (Karpas 299, SU-DHL1) were activated by their cognate ligand Jagged1. As expected, stimulation of tumor cells resulted in an exponential increase in growth rates. This increase could efficiently be blocked by DAPT in a dose-dependent manner indicating that this novel gamma-secretase inhibitor can control tumor cell growth in vitro. We currently investigate whether DAPT potently inhibits Jagged1-induced tumor cell growth in vivo. If so, interruption of Notch signaling by gamma-secretase inhibitors might be a novel therapeutic principle to control the proliferation capacity of neoplasms.

L5 ANSWER 24 OF 29 MEDLINE on STN

ACCESSION NUMBER: 2001390841 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11444983
TITLE: Aspartyl protease inhibitor pepstatin binds to the presenilins of Alzheimer's disease.
AUTHOR: Evin G; Sharples R A; Weidemann A; Reinhard F B; Carbone V; Culvenor J G; Holsinger R M; Sernee M F; Beyreuther K; Masters C L
CORPORATE SOURCE: Department of Pathology, The University of Melbourne, Parkville, Victoria 3010, Australia.. gmevin@unimelb.edu.au
SOURCE: Biochemistry, (2001 Jul 27) Vol. 40, No. 28, pp. 8359-68. Journal code: 0370623. ISSN: 0006-2960.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200110

ENTRY DATE: Entered STN: 15 Oct 2001
Last Updated on STN: 15 Oct 2001
Entered Medline: 11 Oct 2001

AB Mutations in the presenilin genes PS1 and PS2 cause early-onset Alzheimer's disease by altering gamma-secretase cleavage of the amyloid precursor protein, the last step in the generation of Abeta peptide. Ablation of presenilin (PS) genes, or mutation of two critical aspartates, abolishes gamma-secretase cleavage, suggesting that PS may be the gamma-secretases. Independently, inhibition experiments indicate that gamma-secretase is an aspartyl protease. To characterize the putative gamma-secretase activity associated with presenilins, lysates from human neuroblastoma SH-SY5Y and human brain homogenates were incubated with biotin derivatives of pepstatin, followed by immunoprecipitation of PS and associated proteins, and biotin detection by Western blotting. Precipitation with PS1 antibodies, directed to either N-terminal or loop regions, yielded the same 43 kDa band, of apparent molecular mass consistent with that of full-length PS1, although it may represent an aspartyl protease complexed with PS1. Incubation of cell lysates with pepstatin-biotin, followed by streptavidin precipitation and PS1 Western blotting, revealed PS1 fragments and full-length protein, indicating that pepstatin-biotin bound to both cleaved and uncleaved PS1. Binding could be competed by gamma-secretase inhibitor L-685,
458 and could not be achieved with a PS1 mutant lacking the two transmembrane aspartates. Pepstatin-biotin was also shown to bind to PS2. PS1 was specifically absorbed to pepstatin-agarose, with an optimal pH of 6. Binding of pepstatin-biotin to PS1 from lymphocytes of a heterozygous carrier of pathologic exon 9 deletion was markedly decreased as compared to control lymphocytes, suggesting that this PS1 mutation altered the pepstatin binding site.

L5 ANSWER 25 OF 29 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN

ACCESSION NUMBER: 1991:457539 BIOSIS
DOCUMENT NUMBER: PREV199192102319; BA92:102319
TITLE: CONFORMATIONAL ANALYSIS OF LIPOPHILIC ANTIFOLATES CRYSTAL STRUCTURE OF 2 AMINO-4-OXO-6-ADAMANTYLPTERIDINE AND A COMPARISON OF ITS BINDING TO BACTERIAL AND AVIAN DIHYDROFOLATE REDUCTASE.
AUTHOR(S): MCCOURT M [Reprint author]; CODY V
CORPORATE SOURCE: MED FOUND BUFFALO, 73 HIGH ST, BUFFALO, NY 14203, USA
SOURCE: Journal of the American Chemical Society, (1991) Vol. 113, No. 17, pp. 6634-6639.
CODEN: JACSAT. ISSN: 0002-7863.
DOCUMENT TYPE: Article
FILE SEGMENT: BA
LANGUAGE: ENGLISH
ENTRY DATE: Entered STN: 11 Oct 1991
Last Updated on STN: 11 Oct 1991

AB The crystal structure of 2-amino-4-oxo-6-adamantylpteridine (DOPT), a folate analogue of the potent lipophilic antifolate, 2,4-diamino-6-adamantylpteridine (DAPT), which is selective for mammalian dihydrofolate reductase (DHFR), was determined to examine its conformational features and to define its mode of binding to the enzyme DHFR. DOPT crystallized as an ethanesulfonate salt in the monoclinic space group P21/c with cell dimensions a = 20.261 (7) Å, b = 16.357 (2) Å, c = 12.317 (3) Å, β = 9.376 (2)°, and Z = 8.
The pteridine ring is protonated at N(1) to from the ethanesulfonate salt. A theoretical study of the binding characteristics of the folate, DOPT, the antifolate model, DAPT, and the pyrimidine analogue, 2,4-diamino-5-adamantyl-6-methylpyrimidine, DAMP, to both chicken and Lactobacillus casei DHFR was carried out with YETI, a molecular mechanics program which optimized the DHFR-inhibitor interactions. The objective of these calculations was to determine characteristics of binding that would aid in the explaining the species specificity and selectivity of DAMP and DAPT. These studies indicate that there is a correlation between

the size of a specific enzyme active site and antifolate activity, i.e., the antifolates DAPT and DAMP have more unfavorable intermolecular interactions in the bacterial enzyme than in chicken liver DHFR, consistent with their biological activity. These studies further indicate that DOPT, the oxidized analogue of DAPT, is not likely to bind in the folate orientation.

L5 ANSWER 26 OF 29 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 1975:103536 BIOSIS
DOCUMENT NUMBER: PREV197559003536; BA59:3536
TITLE: IMMUNOLOGIC STUDY OF AN ONCORNAVIRUS ISOLATED FROM A HUMAN CANCER CELL LINE.
AUTHOR(S): ILYIN K V; IRLIN I S; BYKOVSKY A F; SPURE Z Z; MILLER G G; ABENOVA U A; ZHDANOV V M
SOURCE: Cancer, (1974) Vol. 34, No. 3, pp. 532-538.
CODEN: CANCAR. ISSN: 0008-543X.
DOCUMENT TYPE: Article
FILE SEGMENT: BA
LANGUAGE: Unavailable

L5 ANSWER 27 OF 29 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 1974:214823 BIOSIS
DOCUMENT NUMBER: PREV197458044517; BA58:44517
TITLE: A STUDY OF GROUP SPECIFIC ANTIGEN OF ONCORNAVIRUS FROM HUMAN LARYNX CARCINOMA CELLS AND ITS COMPARISON WITH ANTIGENS OF ONCORNAVIRUSES OF DIFFERENT ORIGINS.
AUTHOR(S): IL'IN K V; IRLIN I S; BYKOVSKII A F; SPURE ZH ZH; MILLER G G; ZHDANOV V M
SOURCE: Voprosy Virusologii, (1974) No. 1, pp. 57-60.
CODEN: VVIRAT. ISSN: 0507-4088.
DOCUMENT TYPE: Article
FILE SEGMENT: BA
LANGUAGE: Unavailable

L5 ANSWER 28 OF 29 CAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 5
ACCESSION NUMBER: 1974:532592 CAPLUS
DOCUMENT NUMBER: 81:132592
TITLE: Biological characteristics of the B-type oncornaviruses isolated from inoculated cell lines of human carcinomas
AUTHOR(S): Zhdanov, V. M.; Bykovskii, A. F.; Il'in, K. V.
CORPORATE SOURCE: Inst. Virusol. im. Ivanovskogo, Moscow, USSR
SOURCE: Vestnik Akademii Meditsinskikh Nauk SSSR (1974), (3), 3-13
CODEN: VAMNAQ; ISSN: 0002-3027
DOCUMENT TYPE: Journal
LANGUAGE: Russian
AB Eight strains of viruses were isolated from the lines and sublines of inoculated cells of carcinoma of the larynx (Hep-2), carcinoma of the uterine cervix (HeLa) and dedifferentiated astrocytoma (DAPT) in man which morphol., biophys., and biochem. were classified as B-type oncornaviruses. The size of the viruses isolated was of 1000-1500 Å, their floating d. 1.16-1.17 f/ml in gradients of sucrose, RNA with a sedimentation constant of 70S; reproduction of virus was inhibited with D actinomycin; the virions contain reverse transcriptase. The strains of the virus under study were not pathogenic for mice and immunol. differ from the virus of cancer of the mammary gland in mice (Bittner's virus).

L5 ANSWER 29 OF 29 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN DUPLICATE 6
ACCESSION NUMBER: 1974:173916 BIOSIS
DOCUMENT NUMBER: PREV197458003610; BA58:3610

TITLE: B TYPE ONCORNAVIRUSES ISOLATED FROM CONTINUOUS HUMAN CANCER CELL LINES.
AUTHOR(S): BYKOVSKY A F; MILLER G G; YERSHOV F I; ILYIN K V; ZHDANOV V M
SOURCE: Archiv fuer die Gesamte Virusforschung, (1973) Vol. 42, No. 1, pp. 21-35.
DOCUMENT TYPE: Article
FILE SEGMENT: BA
LANGUAGE: Unavailable

=> secretase (3a) l4
PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH
FIELD CODE - 'AND' OPERATOR ASSUMED 'SECRETASE (3A) L12'
PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH
FIELD CODE - 'AND' OPERATOR ASSUMED 'SECRETASE (3A) L13'
PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH
FIELD CODE - 'AND' OPERATOR ASSUMED 'SECRETASE (3A) L14'
PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH
FIELD CODE - 'AND' OPERATOR ASSUMED 'SECRETASE (3A) L15'
L6 27 SECRETASE (3A) L4

=> secretase and l4
L7 27 SECRETASE AND L4

=> dup rem l7
PROCESSING COMPLETED FOR L7
L8 20 DUP REM L7 (7 DUPLICATES REMOVED)

=> d ibib abs total

L8 ANSWER 1 OF 20 CAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 1
ACCESSION NUMBER: 2006:503072 CAPLUS
TITLE: Collagen type I selectively activates ectodomain shedding of the discoidin domain receptor 1: involvement of Src tyrosine kinase
AUTHOR(S): Slack, Barbara E.; Siniaia, Marina S.; Blusztajn, Jan K.
CORPORATE SOURCE: Department of Pathology and Laboratory Medicine, Boston University School of Medicine, Boston, MA, 02118, USA
SOURCE: Journal of Cellular Biochemistry (2006), 98(3), 672-684
CODEN: JCEBD5; ISSN: 0730-2312
PUBLISHER: Wiley-Liss, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The discoidin domain receptor 1 (DDR1) is a receptor tyrosine kinase that is highly expressed in breast carcinoma cells. Upon binding to collagen, DDR1 undergoes autophosphorylation followed by limited proteolysis to generate a tyrosine phosphorylated C-terminal fragment (CTF). Although it was postulated that this fragment is formed as a result of shedding of the N-terminal ectodomain, collagen-dependent release of the DDR1 extracellular domain has not been demonstrated. We now report that, in conjunction with CTF formation, collagen type I stimulates concentration-dependent, saturable shedding of the DDR1 ectodomain from two carcinoma cell lines, and from transfected cells. In contrast, collagen did not promote cleavage of other transmembrane proteins including the amyloid precursor protein (APP), ErbB2, and E-cadherin. Collagen-dependent tyrosine phosphorylation and proteolysis of DDR1 in carcinoma cells were reduced by a pharmacol. Src inhibitor. Moreover, expression of a dominant neg. Src mutant protein in human embryonic kidney cells inhibited collagen-dependent phosphorylation and shedding of co-transfected DDR1. The hydroxamate-based metalloproteinase inhibitor TAPI-1 (tumor necrosis factor-α protease inhibitor-1), and

tissue inhibitor of metalloproteinase (TIMP)-3, also blocked collagen-evoked DDR1 shedding, but did not reduce levels of the phosphorylated CTF. Neither shedding nor CTF formation were affected by the γ- secretase inhibitor, L-685,
458. The results demonstrate that collagen-evoked ectodomain cleavage of DDR1 is mediated in part by Src-dependent activation or recruitment of a matrix- or disintegrin metalloproteinase, and that CTF formation can occur independently of ectodomain shedding. Delayed shedding of the DDR1 ectodomain may represent a mechanism that limits DDR1-dependent cell adhesion and migration on collagen matrixes.

REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 2 OF 20 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:76375 CAPLUS
DOCUMENT NUMBER: 142:148791
TITLE: Compounds and methods for promoting angiogenesis using a γ- secretase inhibitor or inhibiting the γ- secretase pathway
INVENTOR(S): Hellstrom, Mats; Karlsson, Linda; Wallgard, Elisabet
PATENT ASSIGNEE(S): Angiogenetics Sweden AB, Swed.
SOURCE: PCT Int. Appl., 29 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005008250	A1	20050127	WO 2004-SE1146	20040721
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
EP 1671129	A1	20060621	EP 2004-749182	20040721
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, FI, RO, CY, TR, BG, CZ, EE, HU, PL, SK				

PRIORITY APPLN. INFO.:

SE 2003-2111	A	20030721
US 2003-488345P	P	20030721
WO 2004-SE1146	W	20040721

AB Angiogenesis may be initiated or increased through the use of γ- secretase inhibitors. The γ- secretase inhibitor DAPT (N-[N-(3,5-Difluorophenacetyl-L-alanyl)]-S-phenylglycine t-Bu Ester) can initiate and increase angiogenesis . Methods for initiating and increasing angiogenesis are used for disease prevention and treatment as well as for generating research models.

REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 3 OF 20 MEDLINE on STN
ACCESSION NUMBER: 2005135165 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15766262
TITLE: Transition-state analogue gamma-secretase inhibitors stabilize a 900 kDa presenilin/nicastrin complex.

AUTHOR: Evin Genevieve; Canterford Louise D; Hoke David E; Sharples Robyn A; Culvenor Janetta G; Masters Colin L
CORPORATE SOURCE: Department of Pathology, The University of Melbourne, Parkville 3010, and The Mental Health Research Institute, Parkville 3052, Australia.. gmevin@unimelb.edu.au
CONTRACT NUMBER: AG05887 (NIA)
SOURCE: Biochemistry, (2005 Mar 22) Vol. 44, No. 11, pp. 4332-41. Journal code: 0370623. ISSN: 0006-2960.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200505
ENTRY DATE: Entered STN: 16 Mar 2005
Last Updated on STN: 26 May 2005
Entered Medline: 25 May 2005

AB Gamma-secretase mediates the final step, which generates Alzheimer's disease Abeta amyloid protein, by cleaving the transmembrane domain of the amyloid-beta protein precursor. Four gene products, presenilin, nicastrin, APH-1, and PEN-2, are required for gamma-secretase activity that is contained within a high molecular mass complex. To further characterize gamma-secretase, we probed membranes from human neuroblastoma SH-SY5Y cells with gamma-secretase inhibitor biotin derivatives of L-685 ,458, pepstatin A, and the difluoro alcohol 1-Bt. These inhibitor derivatives bound and precipitated PS1 fragments from membrane CHAPSO extracts. Analysis of PS1 complexes by blue native gel electrophoresis and western blotting indicated that the CHAPSO extracts contained complexes of approximately 900, 500, and 400 kDa. With this technique, derivatives of the three inhibitors were detected only in association with the 900 kDa species. Size-exclusion chromatography showed that 13% of PS1 immunoreactivity extracted with CHAPSO was comprised within a >or=900 kDa species with the remaining eluting in fractions of 669-250 kDa but that most enzymatic activity was associated with the 900 kDa fractions. After treatment with L-685 ,458 inhibitor, 49% PS1 immunoreactivity was eluted in the 900 kDa fraction, supporting evidence that the inhibitor stabilized this complex. Subcellular fractionation of SH-SY5Y cells indicated that the 900 kDa complex was formed as PS1 and NCT matured through the secretory pathway and that enzymatic activity correlated with complex maturation. From these observations, we propose a model for the structure of active gamma-secretase that would consist of dimerization of 400-500 kDa subunits and be consistent with the apparent molecular mass of the complex.

L8 ANSWER 4 OF 20 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:524116 CAPLUS
DOCUMENT NUMBER: 143:419827
TITLE: Inducible nitric oxide synthase up-regulates Notch-1 in mouse cholangiocytes: implications for carcinogenesis
AUTHOR(S): Ishimura, Norihisa; Bronk, Steven F.; Gores, Gregory J.
CORPORATE SOURCE: Division of Gastroenterology and Hepatology, Mayo Clinic, College of Medicine, Rochester, MN, USA
SOURCE: Gastroenterology (2005), 128(5), 1354-1368 CODEN: GASTAB; ISSN: 0016-5085
PUBLISHER: Elsevier Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Inflammatory mediators and cell fate genes, such as the Notch gene family, both have been implicated in cancer biol. Because cholangiocarcinomas arise in a background of inflammation and express the inflammatory mediator inducible nitric oxide synthase (iNOS), we aimed to determine whether iNOS expression alters Notch expression and signaling. Notch

receptor and ligand expression in human liver was evaluated by immunohistochem. The effect of iNOS and NO on Notch-1 expression was examined in cell lines. Notch-1, but not other Notch receptors, were up-regulated by cholangiocytes in primary sclerosing cholangitis and cholangiocarcinoma. The colocalization of Notch-1 and iNOS also was observed in large bile ducts from the hilar region of primary sclerosing cholangitis patients. Notch-1 expression in murine cholangiocytes was iNOS dependent. INOS expression also facilitated Notch signaling by inducing the nuclear translocation of its intracellular domain and the expression of a transcriptional target, hairy and enhancer of split (Hes)-1. The γ- secretase inhibitor N-[N-(3,5-Difluorophenacetyl-L-alanyl)-S-phenylglycine]t-Bu ester, which blocks Notch signaling, enhanced tumor necrosis factor-related apoptosis-inducing ligand-induced apoptosis in cholangiocarcinoma cells. These data implicate a direct link between the inflammatory mediator iNOS and Notch signaling, and have implications for the development and progression of cholangiocarcinoma.

REFERENCE COUNT: 52 THERE ARE 52 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 5 OF 20 CAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 2

ACCESSION NUMBER: 2005:1210892 CAPLUS
DOCUMENT NUMBER: 144:48725
TITLE: Blockade of γ- secretase activity within the hippocampus enhances long-term memory
AUTHOR(S): Dash, Pramod K.; Moore, Anthony N.; Orsi, Sara A.
CORPORATE SOURCE: The Vivian L. Smith Center for Neurologic Research and Department of Neurobiology and Anatomy, The University of Texas Medical School, Houston, TX, 77225, USA
SOURCE: Biochemical and Biophysical Research Communications (2005), 338(2), 777-782
CODEN: BBRCA9; ISSN: 0006-291X
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The γ- secretase complex, a membrane-bound aspartyl protease, hydrolyzes the transmembrane domains of several integral membrane proteins including the key signaling mols. amyloid precursor protein (APP), Notch, deleted in colorectal cancer (DCC), and N- and E-cadherins. The proteolysis processing of these proteins is critical for generation of signaling mols. that may participate in neuronal communication and plasticity. Using a potent γ- secretase inhibitor, L-685,458, we examined if blockade of its activity in the hippocampus can influence contextual and spatial memory in rats. Surprisingly, we observed that post-training blockade of γ- secretase activity leads to enhanced long-term memory in two hippocampus-dependent tasks. This suggests that a signaling mol.(s) generated by γ- secretase activity may have a neg. influence on long-term memory formation.

REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 6 OF 20 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2005:151648 CAPLUS
DOCUMENT NUMBER: 142:456393
TITLE: Effects of the histone deacetylase inhibitor valproic acid on Notch signalling in human neuroblastoma cells
AUTHOR(S): Stockhausen, M-T.; Sjoelund, J.; Manetopoulos, C.; Axelson, H.
CORPORATE SOURCE: Department of Laboratory Medicine, Division of Molecular Medicine, Lund University, Malmoe, S-205 02, Swed.
SOURCE: British Journal of Cancer (2005), 92(4), 751-759
CODEN: BJCAAI; ISSN: 0007-0920
PUBLISHER: Nature Publishing Group

DOCUMENT TYPE: Journal
LANGUAGE: English
AB Neuroblastoma (NB), a sympathetically derived childhood tumor, shows characteristics of neuronal precursor cells, suggesting a halted differentiation process. We have previously shown that the Notch signalling cascade, a key player during normal neurogenesis, also might be involved in NB differentiation. Valproic acid (VPA), a well-tolerated antiepileptic drug, has been shown to induce differentiation and cell death of NB cells, possibly associated with its recently described HDAC inhibiting activity. Stimulation of NB cells with VPA led to increased cell death and phenotypic changes associated with differentiation, i.e., neurite extension and upregulation of neuronal markers. VPA treatment also led to an activated Notch signalling cascade as shown by increased levels of intracellular Notch-1 and Hes-1, mimicking the initial phase of induced differentiation. These results reinforce that VPA potentially could be used in differentiation therapy of NB and that the effects in part could be a consequence of interference with the Notch signalling cascade.
REFERENCE COUNT: 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 7 OF 20 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 2006:182870 BIOSIS
DOCUMENT NUMBER: PREV200600184982
TITLE: Identification of ID4 as a cooperating second hit for T cell lymphoma development in PU.1 URE Delta/Delta mice.
AUTHOR(S): Owens, Bronwyn M. [Reprint Author]; Yu, Li; Steidl, Ulrich; Kutok, Jeffrey L.; Clayton, Linda K.; Wagner, Katharina; Iwasaki, Hiromi; Liu, Chunhui; Hackanson, Bibrn; Akashi, Koichi; Plass, Christoph; Tenen, Daniel G.; Rosenbauer, Frank
CORPORATE SOURCE: Harvard Univ, Inst Med, Boston, MA 02115 USA
SOURCE: Blood, (NOV 16 2005) Vol. 106, No. 11, Part 1, pp. 734A-735A.
Meeting Info.: 47th Annual Meeting of the American-Society-of-Hematology. Atlanta, GA, USA. December 10 -13, 2005. Amer Soc Hematol.
CODEN: BLOOAW. ISSN: 0006-4971.
DOCUMENT TYPE: Conference; (Meeting)
Conference; (Meeting Poster)
LANGUAGE: English
ENTRY DATE: Entered STN: 15 Mar 2006
Last Updated on STN: 15 Mar 2006
AB NOTCH1 was discovered through its involvement in the t(7;9) chromosomal translocation found in less than 1% of T-ALLs. Recent studies have demonstrated a broader involvement of NOTCH1 in human T-ALL. The majority of T-ALL patients have activating mutations that disrupt either the heterodimerization domain or the PEST domain of NOTCH1. We sought to determine whether these mutations are also acquired in mouse models of T-ALL. We have sequenced the heterodimerization domain and PEST domain of notch1 in our mouse model of TAL1-induced leukemia and have found that 74% of the tumors harbor activating mutations in notch1. Cell lines derived from these tumors undergo G(0)/G(1) arrest and often apoptosis when treated with a gamma-secretase inhibitor (DAPT). In addition, we found activating notch1 mutations in 38% of thymic lymphomas that occur in mice deficient for various combinations of the H2AX, p53 and Rag2 genes. Thus, notch1 mutations are often acquired as a part of the molecular pathogenesis of T-ALL occurring in mice predisposed to develop the disease because they are transgenic for overexpression of the tall oncogene or because they have lost key tumor suppressor genes known to promote genomic instability.

L8 ANSWER 8 OF 20 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 2006:182866 BIOSIS
DOCUMENT NUMBER: PREV200600184978

TITLE: Activating Notch1 mutations in mouse models of T-ALL.
AUTHOR(S): O'Neil, Jennifer [Reprint Author]; Calvo, Jennifer; McKenna, Keith; Krishnamoorthy, Veena; Aster, Jon C.; Bassing, Craig H.; Alt, Frederick W.; Kelliher, Michelle; Look, A. Thomas
CORPORATE SOURCE: Dana Farber Canc Inst, Dept Pediat Oncol, Boston, MA 02115 USA
SOURCE: Blood, (NOV 16 2005) Vol. 106, No. 11, Part 1, pp. 734A. Meeting Info.: 47th Annual Meeting of the American-Society-of-Hematology. Atlanta, GA, USA. December 10 -13, 2005. Amer Soc Hematol.
CODEN: BLOOAW. ISSN: 0006-4971.
DOCUMENT TYPE: Conference; (Meeting)
Conference; (Meeting Poster)
LANGUAGE: English
ENTRY DATE: Entered STN: 15 Mar 2006
Last Updated on STN: 15 Mar 2006

AB NOTCH1 was discovered through its involvement in the t(7;9) chromosomal translocation found in less than 1% of T-ALLs. Recent studies have demonstrated a broader involvement of NOTCH1 in human T-ALL. The majority of T-ALL patients have activating mutations that disrupt either the heterodimerization domain or the PEST domain of NOTCH1. We sought to determine whether these mutations are also acquired in mouse models of TALL. We have sequenced the heterodimerization domain and PEST domain of notchI in our mouse model of TALI-induced leukemia and have found that 74% of the tumors harbor activating mutations in notch1. Cell lines derived from these tumors undergo G(0)/G(1), arrest and often apoptosis when treated with a gamma-secretase inhibitor (DAPT). In addition, we found activating notch1 mutations in 38% of thymic lymphomas that occur in mice deficient for various combinations of the H2AX, p53 and Rag2 genes. Thus, notch1 mutations are often acquired as a part of the molecular pathogenesis of T-ALL occurring in mice predisposed to develop the disease because they are transgenic for overexpression of the tall oncogene or because they have lost key tumor suppressor genes known to promote genomic instability.

L8 ANSWER 9 OF 20 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 2006:181221 BIOSIS
DOCUMENT NUMBER: PREV200600183333
TITLE: Quantitative proteomic studies of gamma-secretase inhibition in Hodgkin lymphoma cells reveal novel insights into notch signaling.
AUTHOR(S): Wallentine, Jeremy C. [Reprint Author]; Crockett, David K.; Elenitoba-Johnson, Kojo S. J.; Lim, Megan S.
CORPORATE SOURCE: Univ Utah, Dept Pathol, Sch Med, Salt Lake City, UT 84112 USA
SOURCE: Blood, (NOV 16 2005) Vol. 106, No. 11, Part 1, pp. 283A. Meeting Info.: 47th Annual Meeting of the American-Society-of-Hematology. Atlanta, GA, USA. December 10 -13, 2005. Amer Soc Hematol.
CODEN: BLOOAW. ISSN: 0006-4971.
DOCUMENT TYPE: Conference; (Meeting)
Conference; (Meeting Poster)
LANGUAGE: English
ENTRY DATE: Entered STN: 15 Mar 2006
Last Updated on STN: 15 Mar 2006

AB Notch signaling has been implicated in the regulation of Hodgkin lymphoma (HL) survival via NF-kappaB. Notch signaling is dependent on the interaction of ligands with the transmembrane notch receptor. Ligand binding triggers proteolytic cleavage of the intracellular notch domain with subsequent translocation to the nucleus and activation of transcription factors. Gamma-secretase which catalyzes the protenlytic cleavage and release of the notch intracellular domain is critical in the mediation of notch signaling. Inhibition of gamma-secretase using 7 (N-[N-(3,5-difluorophenyl)-L-alanyl]-s-phenyl-

glycine t-butyl ester) (DAFT) in rat fetal thymocytes significantly reduces the expression of notch target genes. We identified proteins released by HL-derived cells into conditioned media including multiple upstream and downstream components of the notch signaling cascade, specifically: notch 1, notch2, jagged1, jagged2, HES2, Hes4, GATA2 and GATA5. A proteomic analysis of the differentially expressed proteins among DAFT treated and untreated cells will reveal potential novel downstream mediators of notch signaling, increasing our understanding of HL pathogenesis. We sought to identify the proteomic consequences of notch signaling inhibition in L428 HL cells using a mass spectrometry-based proteomic approach. Treatment of L428 HL cells with DART (50 mu M) resulted in decreased cell proliferation as measured by the MTT assay which was associated with induction of p27Kip1. We utilized an endoproteinase catalyzed O16/O18 differential isotopic strategy to quantitatively determine the global proteomic changes following inhibition of the notch signaling pathway using DAFT. Proteins were collected from the cell lysate of treated and non-treated L428 cells, subjected to O16/O18 labeling and then analyzed by reverse-phase liquid chromatography coupled with electrospray ionization tandem mass spectrometry. A total of 156 proteins with 2 or more unique peptides were identified as being differentially expressed between treated and non-treated L428 cells. Proteins of diverse location and function were identified. Importantly a large number of proteins involved in transcription (12%; RelB, TRRAP, RB-associated protein, NCOR1), and located in the nucleus (27%; H2AO, FUSE binding protein 1, ANC5, SMYD1) were identified. Other important functional categories of the identified proteins included signaling activity (28%), and catalytic activity (41%). Several known proteins regulated by notch and involved with the regulation of notch activity such as (Histone acetyltransferase PCAF, RelB. N-COR1) were identified and found to be under expressed in treated cells. In addition, novel proteins with transcriptional and cell signaling activities have been identified, representing unique pathways that may be directly or indirectly affected by notch signaling. Our study represents the first comprehensive analysis of differentially expressed proteins following the inhibition of notch signaling. These results provide novel insights into our understanding of the pathogenesis and the role of notch signaling in HL.

L8 ANSWER 10 OF 20 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:387245 CAPLUS
DOCUMENT NUMBER: 143:625
TITLE: Inhibition of angiogenesis and tumor growth by β and γ- secretase inhibitors
AUTHOR(S): Paris, Daniel; Quadros, Amita; Patel, Nikunj; DelleDonne, Anthony; Humphrey, James; Mullan, Michael
CORPORATE SOURCE: Roskamp Institute, Sarasota, FL, 34243, USA
SOURCE: European Journal of Pharmacology (2005), 514(1), 1-15
CODEN: EJPHAZ; ISSN: 0014-2999
PUBLISHER: Elsevier B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The involvement of β- secretase and γ- secretase in producing the β-amyloid component of senile plaques found in the brain of Alzheimer's patients has fueled a major research effort to design selective inhibitors of these proteases. Interestingly, γ- secretase cleaves several proteins including Notch, E-cadherin, CD44 and ErbB-4 (erythroblastic leukemia viral oncogene homolog 4), which are important modulators of angiogenesis. The β-amyloid precursor protein, which is cleaved by β- secretase and γ- secretase to produce β-amyloid, is highly expressed in the endothelium of neoforming vessels suggesting that it might play a role during angiogenesis. These data prompted us to explore the effects of β and γ- secretase inhibitors of different structures on angiogenesis and tumor growth. Both the γ

and β- secretase inhibitors tested reduce endothelial cell proliferation without inducing cellular toxicity, suppress the formation of capillary structures in vitro and oppose the sprouting of microvessel outgrowths in the rat aortic ring model of angiogenesis. Moreover, they potently inhibit the growth and vascularization of human glioblastoma and human lung adenocarcinoma tumors xenotransplanted into nude mice. Altogether these data suggest that the γ and β- secretases play an essential role during angiogenesis and that inhibitors of the β and γ-secretases may constitute new classes of anti-angiogenic and anti-tumoral compds.

REFERENCE COUNT: 51 THERE ARE 51 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 11 OF 20 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:718305 CAPLUS
DOCUMENT NUMBER: 141:236630
TITLE: Anti-angiogenic and anti-tumoral properties of beta and gamma secretase inhibitors
INVENTOR(S): Paris, Daniel; Mullan, Michael J.
PATENT ASSIGNEE(S): Roskamp Research LLC, USA
SOURCE: PCT Int. Appl., 44 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004073630	A2	20040902	WO 2004-US4494	20040218
WO 2004073630	A3	20050428		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI				
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2004212965	A1	20040902	AU 2004-212965	20040218
CA 2516259	AA	20040902	CA 2004-2516259	20040218
US 2004229816	A1	20041118	US 2004-780905	20040218
EP 1596878	A2	20051123	EP 2004-712274	20040218
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
BR 2004007597	A	20060221	BR 2004-7597	20040218
CN 1777436	A	20060524	CN 2004-80010480	20040218
JP 2006517979	T2	20060803	JP 2006-503611	20040218
NO 2005004221	A	20051111	NO 2005-4221	20050912
PRIORITY APPLN. INFO.:			US 2003-319954P P	20030218
			WO 2004-US4494 A	20040218

AB The present invention relates to methods of treating tumors or proliferative disorders that are associated with angiogenesis by administering g-secretase and b-secretase inhibitors that inhibit secretases involved in amyloid precursor protein processing. In particular, methods are provided to treat tumors or proliferative disorders, or to inhibit angiogenesis associated with tumors, proliferative or inflammatory disorders, in animals or humans in need of such treatment or angiogenic inhibition, by administering to the animal or human therapeutically effective amts. in unit dosage form of a composition containing a carrier and at least one g-secretase or b-secretase inhibitor that inhibits secretase APP processing.

L8 ANSWER 12 OF 20 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN

ACCESSION NUMBER: 2005:477542 BIOSIS
DOCUMENT NUMBER: PREV200510269446
TITLE: Notch signaling-dependant expulsion of parasites through mast cell-mediated immunity.
AUTHOR(S): Sakata-Yanagimoto, Mamiko [Reprint Author]; Yamaguchi-Nakagami, Etsuko; Sakai, Toru; Kumano, Keiki; Kunisato, Atsushi; Crcareva, Aleksandra; Kurokawa, Mineo; Ogawa, Seishi; Yasutomo, Koji; Hirai, Hisamaru; Chiba, Shigeru
CORPORATE SOURCE: Tokyo Univ Hosp, Dept Cell Therapy Transplantat Med, Tokyo 113, Japan
SOURCE: Blood, (NOV 16 2004) Vol. 104, No. 11, Part 1, pp. 412A. Meeting Info.: 46th Annual Meeting of the American-Society-of-Hematology. San Diego, CA, USA. December 04 -07, 2004. Amer Soc Hematol. CODEN: BLOOAW. ISSN: 0006-4971.
DOCUMENT TYPE: Conference; (Meeting)
Conference; (Meeting Poster)
LANGUAGE: English
ENTRY DATE: Entered STN: 16 Nov 2005
Last Updated on STN: 16 Nov 2005

AB [Background] Notch signaling is known to be important in hematopoiesis, but very little information is available about its significance in mast cells. Here we provide direct evidence that notch signaling is critical for both development and function of mast cells in vitro and in vivo. [Methods] A Lin(-) fraction of mouse bone marrow cells was cultured on immobilized Delta1 in the presence of SCF and IL-3, and emerging Lin(-)Fc epsilon RI(+)c-Kit(+) mast cells were characterized. Next, production of mouse mast cell protease-1 (mMCP-1), which is specific for nematode infection through locally expressed TGF-beta 1 in vivo, by bone marrow-derived mast cells (BMMC) was analyzed after the stimulation with Delta1 in the presence of TGF-beta 1. Finally, mice were infected with Strongyloides venezuelensis after pre-treatment with Delta1, and expulsion of the worms was examined. [Results] Lin(-)Fc epsilon RI(+)c-Kit(+) mast cells developed remarkably earlier if stimulated with Delta1 (at one week, 15% vs. 3%). DAPT, a gamma-secretase inhibitor, blocked the Delta1 effect, while it did not affect the regular time-course mast cell generation by SCF and IL-3. SB431542, a selectiveinhibitor of TGF-1 signaling, also blocked early mast cell generation by Delta1. Delta1 augmented mMCP-1 expression and secretion from BMMC by 50 fold. Both DAPT and SB431542 showed a dose-dependent inhibition of Delta1 effect on mMCP-1 expression and secretion. Pretreatment of the hosts with Delta1 promoted the expulsion of S. venezuelensis, (left/inoculated ratios of worms, 3% vs. 40%) while Delta1 had no effect in the mast cell-deficient W/Wv mice. [Discussion] Our observations reveal that notch signaling regulates both development and function of mast cells in vitro in conjunction with TGF-beta 1 signaling. In vivo, it is also likely that Delta1 facilitates the functional maturation of intestinal mast cells to eradicate parasites. More precise mechanism of Delta1 action on mast cells in vivo is under a study.[GRAPHICS]These purified monocytes also showed transdifferentiation into endothelial cells in the presence of PTN with m-CSF unlike cells treated with m-CSF-alone orcells without these factors present. We determined whether PTN could also stimulate differentiation of bone marrow stem cells into endothelial cells. The stem cells were derived from bone marrow selected for CD34 using magnetic bead selection, and were stimulated with either m-CSF or PTN alone or a combinationof m-CSF and PTN or no treatment for 7 days. Real time PCR analysis showed that the m-CSF and PTN combination markedly increased endothelial cell marker expression and decreased monocyte marker (CD68 and c-fms) expression in this stem cell population. When induced with PTN alone, the stem cells exhibited slightly increasing expression of endothelial markers with no change in monocyte marker expression whereas m-CSF alone and no treatment had no effect on either endothelial or

monocyte marker expression. These experiments define a previously unrecognized novel mechanism leading to angiogenesis in cancer patients- thetransdifferentiation of monocytes into endothelial cells by a factor highly produced by tumor cells. They also suggest a potential new specific target to inhibit angiogenesis-pleitrophin which may have profound clinical implications.

L8 ANSWER 13 OF 20 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 2004326678 EMBASE
TITLE: Notch signaling in neuroblastoma.
AUTHOR: Pahlman S.; Stockhausen M.-T.; Fredlund E.; Axelson H.
CORPORATE SOURCE: H. Axelson, Department of Laboratory Medicine, Division of Molecular Medicine, Lund Univ., Univ. Hosp. MAS, E., Malmo, Sweden. hakan.axelson@molmed.mas.lu.se
SOURCE: Seminars in Cancer Biology, (2004) Vol. 14, No. 5, pp. 365-373. .
Refs: 60
ISSN: 1044-579X CODEN: SECBE7
PUBLISHER IDENT.: S 1044-579X(04)00033-1
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 008 Neurology and Neurosurgery
021 Developmental Biology and Teratology
022 Human Genetics
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 2 Sep 2004
Last Updated on STN: 2 Sep 2004

AB Neuroblastoma is a pediatric tumor that originates from precursor cells of the sympathetic nervous system that have discontinued their normal differentiation program. This review is focused on involvement of the Notch signaling cascade in the process of differentiation in neuroblastoma cells and normal cells of the sympathetic nervous system. Hypoxia induces dedifferentiation of neuroblastoma cells in vivo and in vitro, and under oxygen-compromised conditions the Notch cascade is activated. This activation might promote development of the dedifferentiated phenotype. The implications of these observations for tumor biology are also discussed. .COPYRGT. 2004 Elsevier Ltd. All rights reserved.

L8 ANSWER 14 OF 20 MEDLINE on STN

ACCESSION NUMBER: 2003100609 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12493731
TITLE: Familial Alzheimer disease-linked presenilin 1 variants enhance production of both Abeta 1-40 and Abeta 1-42 peptides that are only partially sensitive to a potent aspartyl protease transition state inhibitor of "gamma-secretase".
AUTHOR: Ikeuchi Takeshi; Dolios Georgia; Kim Seong-Hun; Wang Rong; Sisodia Sangram S
CORPORATE SOURCE: Department of Neurobiology, Pharmacology and Physiology, The University of Chicago, Chicago, Illinois 60637, USA.
CONTRACT NUMBER: AG021494 (NIA)
AG10491 (NIA)
SOURCE: The Journal of biological chemistry, (2003 Feb 28) Vol. 278, No. 9, pp. 7010-8. Electronic Publication: 2002-12-19.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English

FILE SEGMENT: Priority Journals
ENTRY MONTH: 200304
ENTRY DATE: Entered STN: 5 Mar 2003
Last Updated on STN: 9 Apr 2003
Entered Medline: 8 Apr 2003

AB Presenilin 1 (PS1) plays an essential role in intramembranous "gamma-secretase" processing of several type I membrane proteins, including the beta-amyloid precursor proteins (APP) and Notch1. In this report, we examine the activity of two familial Alzheimer's disease-linked PS1 variants on the production of secreted Abeta peptides and the effects of L-685,458, a potent gamma-secretase inhibitor, on inhibition of Abeta peptides from cells expressing these PS1 variants. We now report that PS1 variants enhance the production and secretion of both Abeta1-42 and Abeta1-40 peptides. More surprisingly, whereas the IC(50) for inhibition of Abeta1-40 peptide production from cells expressing wild-type PS1 is approximately 1.5 microm, cells expressing the PS1deltaE9 mutant PS1 exhibit an IC(50) of approximately 4 microm. Immunoprecipitation and matrix-assisted laser desorption/ionization time-of-flight mass spectrometry reveal that the levels of Abeta1-43 peptides are elevated in medium of PS1deltaE9 cells treated with higher concentrations of inhibitor. The differential effects of wild-type and mutant PS1 on gamma-secretase production of Abeta peptides and the disparity in sensitivity of these peptides to a potent gamma-secretase suggest that PS may be necessary, but not sufficient, to catalyze hydrolysis at the scissile bonds that generate the termini of Abeta1-40 and Abeta1-42 peptides.

L8 ANSWER 15 OF 20 CAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 3
ACCESSION NUMBER: 2003:436167 CAPLUS
DOCUMENT NUMBER: 139:357709
TITLE: Aspartic peptidase inhibitors: Implications in drug development
AUTHOR(S): Dash, Chandravanu; Kulkarni, Aarohi; Dunn, Ben; Rao, Mala
CORPORATE SOURCE: Division of Biochemical Sciences, National Chemical Laboratory, Pune, 411008, India
SOURCE: Critical Reviews in Biochemistry and Molecular Biology (2003), 38(2), 89-119
CODEN: CRBBEJ; ISSN: 1040-9238
PUBLISHER: CRC Press LLC
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. The last decade has witnessed an effervescence of research interest in the development of potent inhibitors of various aspartic peptidases. As an enzyme family, aspartic peptidases are relatively a small group that has received enormous interest because of their significant roles in human diseases like involvement of renin in hypertension, cathepsin D in metastasis of breast cancer, β- Secretase in Alzheimer's Disease, plasmepsins in malaria, HIV-1 peptidase in acquired immune deficiency syndrome, and secreted aspartic peptidases in candidal infections. There have been developments on clin. active inhibitors of HIV-1 peptidase, which have been licensed for the treatment of AIDS. The inhibitors of plasmepsins and renin are considered a viable therapeutic strategy for the treatment of malaria and hypertension. Relatively few inhibitors of cathepsin D have been reported, partly because of its uncertain role as a viable target for therapeutic intervention. The β- secretase inhibitors OM99-2 and OM003 were designed based on the substrate specificity information. The present article is a comprehensive state-of-the-art review describing the aspartic peptidase inhibitors illustrating the recent developments in the area. In addition, the homologies between the reported inhibitor sequences have been analyzed. The understanding of the structure-function relationships of aspartic peptidases and inhibitors will have a direct impact on the design of new inhibitor drugs.

REFERENCE COUNT: 179 THERE ARE 179 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 16 OF 20 MEDLINE on STN
ACCESSION NUMBER: 2003211080 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12732196
TITLE: Contribution of presenilin/gamma-secretase to calsenilin-mediated apoptosis.
AUTHOR: Jo Dong-Gyu; Chang Jae-Woong; Hong Hyun-Seok; Mook-Jung Inhee; Jung Yong-Keun
CORPORATE SOURCE: Department of Life Science, Kwangju Institute of Science and Technology, Kwangju 500-712, Republic of Korea.
SOURCE: Biochemical and biophysical research communications, (2003 May 23) Vol. 305, No. 1, pp. 62-6.
Journal code: 0372516. ISSN: 0006-291X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200306
ENTRY DATE: Entered STN: 7 May 2003
Last Updated on STN: 19 Jun 2003
Entered Medline: 18 Jun 2003

AB Mutant presenilins cause early-onset of familial Alzheimer's disease and render cells vulnerable to apoptosis. Calsenilin/DREAM/KChIP3 is a multifunctional calcium-binding protein that interacts with presenilin and mediates calcium-mediated apoptosis. In the present study, we report that the calsenilin-mediated apoptosis is regulated by presenilin. The expression of calsenilin was highly up-regulated in neuronal cells undergoing Abeta42-triggered cell death. The incidence of calsenilin-mediated apoptosis was diminished in presenilin-1(-/-) mouse embryonic fibroblast cells or neuronal cells stably expressing a loss-of-function presenilin-1 mutant. On the contrary, an array of familial Alzheimer's disease-associated presenilin mutants (gain-of-function) increased calsenilin-induced cell death. Moreover, gamma-secretase inhibitors, including compound E and DAPT, decreased the calsenilin-induced cell death. These results suggest that the pro-apoptotic activity of calsenilin coordinates with presenilin/gamma-secretase activity to play a crucial role in the neuronal death of Alzheimer's disease.

L8 ANSWER 17 OF 20 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 2002:336050 BIOSIS
DOCUMENT NUMBER: PREV200200336050
TITLE: Amyloid-lowering isocoumarins are not direct inhibitors of gamma-secretase.
AUTHOR(S): Esler, William P. [Reprint author]; Das, Chittaranjan [Reprint author]; Campbell, William A. [Reprint author]; Kimberly, W. Taylor [Reprint author]; Kornilova, Anna Y. [Reprint author]; Diehl, Thekla S. [Reprint author]; Ye, Wenjuan [Reprint author]; Ostaszewski, Beth L. [Reprint author]; Xia, Weiming [Reprint author]; Selkoe, Dennis J. [Reprint author]; Wolfe, Michael S. [Reprint author]
CORPORATE SOURCE: Center for Neurologic Diseases, Brigham and Women's Hospital and Harvard Medical School, 77 Avenue Louis Pasteur, Boston, MA, 02115, USA
mwolfe@rics.bwh.harvard.edu
SOURCE: Nature Cell Biology, (May, 2002) Vol. 4, No. 5, pp. E110-E111. print.
ISSN: 1465-7392.
DOCUMENT TYPE: Letter
LANGUAGE: English
ENTRY DATE: Entered STN: 12 Jun 2002

Last Updated on STN: 12 Jun 2002

L8 ANSWER 18 OF 20 MEDLINE on STN
ACCESSION NUMBER: 2002136366 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11851430
TITLE: A novel epsilon-cleavage within the transmembrane domain of the Alzheimer amyloid precursor protein demonstrates homology with Notch processing.
AUTHOR: Weidemann Andreas; Eggert Simone; Reinhard Friedrich B M; Vogel Markus; Paliga Krzysztof; Baier Gottfried; Masters Colin L; Beyreuther Konrad; Evin Genevieve
CORPORATE SOURCE: Zentrum fur Molekulare Biologie Heidelberg, INF 282, 69120 Heidelberg, Germany.
SOURCE: Biochemistry, (2002 Feb 26) Vol. 41, No. 8, pp. 2825-35. Journal code: 0370623. ISSN: 0006-2960.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200203
ENTRY DATE: Entered STN: 2 Mar 2002
Last Updated on STN: 3 Apr 2002
Entered Medline: 28 Mar 2002
AB Proteolytic processing of the transmembrane domain of the amyloid precursor protein (APP) is a key component of Alzheimer's disease pathogenesis. Using C-terminally tagged APP derivatives, we have identified by amino-terminal sequencing a novel cleavage site of APP, at Leu-49, distal to the gamma-secretase site. This was termed -cleavage. Brefeldin A treatment and pulse-chase experiments indicate that this cleavage occurs late in the secretory pathway. The level of -cleavage is decreased by expression of presenilin-1 mutants known to impair Abeta formation, and it is sensitive to the gamma-secretase inhibitors MDL28170 and L-685,458.
Remarkably, it shares similarities with site 3 cleavage of Notch-1: membrane topology, cleavage before a valine, dependence on presenilins, and inhibition profile.

L8 ANSWER 19 OF 20 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 2003:356701 BIOSIS
DOCUMENT NUMBER: PREV200300356701
TITLE: Novel gamma-Secretase Inhibitor DAPT Blocks Activated Notch Signaling and Controls Tumor Cell Growth in Hodgkin and Anaplastic Large Cell Lymphoma.
AUTHOR(S): Jundt, Franziska [Reprint Author]; Arnold, Wolfgang [Reprint Author]; Mathas, Stephan [Reprint Author]; Wolfe, Michael [Reprint Author]; Forster, Reinhold [Reprint Author]; Dorken, Bernd [Reprint Author]
CORPORATE SOURCE: Universitatsklinikum Charite, Campus Virchow-Klinikum, Humboldt University of Berlin, Germany
SOURCE: Blood, (November 16 2002) Vol. 100, No. 11, pp. Abstract No. 594. print.
Meeting Info.: 44th Annual Meeting of the American Society of Hematology. Philadelphia, PA, USA. December 06-10, 2002. American Society of Hematology.
CODEN: BLOOAW. ISSN: 0006-4971.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
Conference; (Meeting Poster)
LANGUAGE: English
ENTRY DATE: Entered STN: 6 Aug 2003
Last Updated on STN: 6 Aug 2003
AB Notch receptors are key regulators of hematopoietic differentiation and development. Notch activation either induces stem cell renewal or differentiation towards lymphoid lineages. Moreover, activation induces

lymphoid precursors to become T cells rather than B cells. Truncated Notch alleles have further been implicated in the development of aggressive human T-cell leukemia. We recently showed, that Notch receptors are highly overexpressed in primary tumor cells of Hodgkin (25/25 cases) and anaplastic large cell (12/12 cases) lymphoma (Blood 2002; 99:3398-3403). In addition, we demonstrated a novel mechanism for the oncogenic capacity of Notch by showing that activation of Notch signaling by its ligand Jagged1, that was expressed in primary tumor cells as well as in neighboring cells in vivo (immunohistology, in situ hybridisation), resulted in dramatic increases in proliferation and apoptosis resistance of tumor cells of Hodgkin and anaplastic large cell lymphoma. Already highly proliferating tumor cells could exponentially increase their proliferation rates up to 2- or even 3-fold in 20h after Notch activation. Therefore, our data provided evidence, that activation of Notch signaling is essential for the growth and survival of the tumor cells in vitro and that inhibition of Notch signaling in vivo might be a novel therapeutic approach in Hodgkin and anaplastic large cell lymphoma. In this study, we established a xenotransplant model in SCID mice, where we injected the Hodgkin cell line KM-H2 subcutaneously. KM-H2 cells were not tumorigenic in SCID mice within three months (0/8 mice). However, activation of Notch signaling by irradiated Jagged1-expressing cells dramatically increased tumor cell growth of KM-H2 cells (8/11 mice). These data indicate that activated Notch signaling essentially contributes to Hodgkin lymphomagenesis in vivo. Furthermore, we used the functional gamma-secretase inhibitor DAPT to block activated Notch signaling in tumor cells of Hodgkin and anaplastic large cell lymphoma. gamma-secretase catalyzes the release of the intracellular domain of Notch that then translocates to the nucleus to activate expression of downstream genes. Inhibition of gamma-secretase activity is currently investigated as a therapeutic strategy in Alzheimer's disease, because gamma-secretase similarly cleaves amyloid precursor proteins to release Abeta peptides, accumulation of which is causally related to Alzheimer's disease. DAPT was already shown to potently reduce beta-amyloid levels in brain in mouse models of Alzheimer's disease. We tested DAPT activity in proliferation assays in which tumor cells of Hodgkin (L1236, HD-LM2) and anaplastic large cell lymphoma (Karpas 299, SU-DHL1) were activated by their cognate ligand Jagged1. As expected, stimulation of tumor cells resulted in an exponential increase in growth rates. This increase could efficiently be blocked by DAPT in a dose-dependent manner indicating that this novel gamma-secretase inhibitor can control tumor cell growth in vitro. We currently investigate whether DAPT potently inhibits Jagged1-induced tumor cell growth in vivo. If so, interruption of Notch signaling by gamma-secretase inhibitors might be a novel therapeutic principle to control the proliferation capacity of neoplasms.

L8 ANSWER 20 OF 20 MEDLINE on STN

ACCESSION NUMBER:	2001390841 MEDLINE
DOCUMENT NUMBER:	PubMed ID: 11444983
TITLE:	Aspartyl protease inhibitor pepstatin binds to the presenilins of Alzheimer's disease.
AUTHOR:	Evin G; Sharples R A; Weidemann A; Reinhard F B; Carbone V; Culvenor J G; Holsinger R M; Sernee M F; Beyreuther K; Masters C L
CORPORATE SOURCE:	Department of Pathology, The University of Melbourne, Parkville, Victoria 3010, Australia.. gmevin@unimelb.edu.au
SOURCE:	Biochemistry, (2001 Jul 27) Vol. 40, No. 28, pp. 8359-68. Journal code: 0370623. ISSN: 0006-2960.
PUB. COUNTRY:	United States
DOCUMENT TYPE:	Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:	English
FILE SEGMENT:	Priority Journals
ENTRY MONTH:	200110

ENTRY DATE: Entered STN: 15 Oct 2001
Last Updated on STN: 15 Oct 2001
Entered Medline: 11 Oct 2001

AB Mutations in the presenilin genes PS1 and PS2 cause early-onset Alzheimer's disease by altering gamma-secretase cleavage of the amyloid precursor protein, the last step in the generation of Abeta peptide. Ablation of presenilin (PS) genes, or mutation of two critical aspartates, abolishes gamma-secretase cleavage, suggesting that PS may be the gamma-secretases. Independently, inhibition experiments indicate that gamma-secretase is an aspartyl protease. To characterize the putative gamma-secretase activity associated with presenilins, lysates from human neuroblastoma SH-SY5Y and human brain homogenates were incubated with biotin derivatives of pepstatin, followed by immunoprecipitation of PS and associated proteins, and biotin detection by Western blotting. Precipitation with PS1 antibodies, directed to either N-terminal or loop regions, yielded the same 43 kDa band, of apparent molecular mass consistent with that of full-length PS1, although it may represent an aspartyl protease complexed with PS1. Incubation of cell lysates with pepstatin-biotin, followed by streptavidin precipitation and PS1 Western blotting, revealed PS1 fragments and full-length protein, indicating that pepstatin-biotin bound to both cleaved and uncleaved PS1. Binding could be competed by gamma-secretase inhibitor L-685,458 and could not be achieved with a PS1 mutant lacking the two transmembrane aspartates. Pepstatin-biotin was also shown to bind to PS2. PS1 was specifically absorbed to pepstatin-agarose, with an optimal pH of 6. Binding of pepstatin-biotin to PS1 from lymphocytes of a heterozygous carrier of pathologic exon 9 deletion was markedly decreased as compared to control lymphocytes, suggesting that this PS1 mutation altered the pepstatin binding site.

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COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	142.76	151.32

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-13.50	-13.50

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